Association Between Thyroid Dysfunction and Breast Cancer Risk Among Adult Women

Thi van Trinh Tran

université PARIS-SACLAY

Association between thyroid dysfunction and breast cancer risk among adult women

Association entre la dysfonction thyroïdienne et le risque de cancer du sein chez la femme adulte

Thèse de doctorat de l'université Paris-Saclay

École doctorale n°570 : Santé publique (EDSP)
Spécialité de doctorat: Santé publique - Epidémiologie
Unité de recherche : Université Paris-Saclay, UVSQ, Inserm, CESP, 94807, Villejuif, France
Référent : Faculté de médecine

Thèse présentée et soutenue à Villejuif, le 02/11/2021, par

Thi Van Trinh TRAN

Composition du Jury

Laurence LEENHARDT PU-PH, Université Paris VI	Présidente
Patrick ARVEUX Directeur de registre, Unisanté Lausanne	Rapporteur & Examinateur
Guy LAUNOY Professeur, Université de Caen	Rapporteur & Examinateur
Marie-Odile BERNIER CR, Institut de Radioprotection et de Sûreté Nucléaire	Examinatrice

Direction de la thèse

Marie-Christine BOUTRON-RUAULT DR, Université Paris Saclay (INSERM U1018)	Directrice de thèse
Neige JOURNY CR, Université Paris Saclay (INSERM U1018)	Co-encadrante de thèse

Thèse de doctorat

NNT : 2021UPASR022

PREFACE

Thyroid dysfunction - hyper- and hypothyroidism – is one of the most common endocrine disorders, especially among women. Both hyperthyroidism and hypothyroidism are associated with a broad range of clinical manifestations and comorbidities, which often require long-term management, and might be involved in the development of breast cancer. Despite experimental evidence, clinical and epidemiological findings on the risk of breast cancer associated with thyroid dysfunction remain controversial, lacking information on possible confounding and mediating factors such as thyroid dysfunction treatments, comorbidities, and breast cancer risk factors. The principal objective of this thesis project was to evaluate breast cancer risk among women with and without thyroid dysfunction, accounting for potentially important confounders and mediators. The underlying hypothesis is that female breast cancer risk increases both with (1) increasing blood levels of thyroid hormones and (2) treatment of hyperthyroidism with radioactive iodine.

This thesis is comprised of a total of six chapters. Chapter I summarizes the current state of knowledge about the association between thyroid dysfunction and breast cancer risk and presents the thesis objectives. The next two chapters describe the data used for this thesis from the UK Biobank cohort and a European pooled cohort of thyroid cancer survivors (Chapter II), and the statistical methods (Chapter III). Chapter IV reports analyses on thyroid dysfunction effects on breast cancer risk, accounting for treatments, reproductive factors, comorbidities, and other health-related factors. Chapter V reports analyses on breast cancer risk associated with radioactive iodine exposure. Finally, chapter VI synthesizes and discusses the main findings of the project, its potential clinical and public health implications, and proposes perspectives for future research.

université PARIS-SACLAY | ÉCOLE DOCTORALE Santé Publique (EDSP)

ABSTRACT

Title: Association between thyroid dysfunction and breast cancer risk among adult women

Keywords: Thyroid dysfunction, hyperthyroidism, hypothyroidism, radioactive iodine, breast cancer, cohorts

Thyroid dysfunction (hyper- and hypothyroidism) is a frequent condition in women aged 40 years and more. Long-term outcomes of thyroid dysfunction remain unclear, with continuing debates on the effect of abnormal thyroid hormone levels and thyroid dysfunction treatments (e.g radioactive iodine - RAI) on cancer risk. Therefore, this thesis project aimed to evaluate the association between the risk of female breast cancer and thyroid dysfunction, while accounting for thyroid dysfunction treatments, comorbidities, and breast cancer risk factors.

The project was mainly based on the UK Biobank (UKB) cohort and data which we have extracted from a systematic review and a meta-analysis on cancer risk associated with thyroid dysfunction in the scientific litterature. The UKB cohort included 273,375 women aged 40-69 years at inclusion between 2006 and 2010. Detailed data on personal and family medical history, medications, lifestyle, reproductive and socioeconomic characteristics were collected. The UKB cohort has been linked to regional and national hospital inpatient databases, cancer and death registries (5,326 incident breast cancer cases were reported during a median follow-up time of 7 years). In the UKB cohort, we found no significant association between breast cancer risk and either overall hyper- or hypothyroidism. However, breast cancer risk was ~40% higher among women treated for hyperthyroidism compared to women with no thyroid dysfunction, regardless of the treatment modality. No increased risk was observed among women without information on treatments, suggesting an effect hyperthyroidism severity and/or etiology.

When combining those results with all evidence currently available in the litterarure, we estimated a pooled risk ratio of 1.15 and 0.86 for hyper- and hypothyroidism (treated or not), respectively, compared to no thyroid dysfunction. Both in the UKB cohort and in our meta-analysis, the risk estimates differed according to the menaupasual status and age at menopause.

In the meta-analysis, breast cancer risk was significantly reduced among premenopausal women with hypothyroidism, and increased, although insignificantly, among postmenopaused women with hyperthyroidism. In the UKB cohort, we found that among women who experienced late menopause, the lower breast cancer risk associated with hypothyroidism disappeared and the higher risk associated with treated hyperthyroidism increased significantly.

The analyses were extended to a European pooled cohort of 8,475 female thyroid cancer survivors treated in France, Italy, and Sweden (335 breast cancer cases were reported during a median follow-up time of 12.7 years), which allowed us to investigate the role of RAI in breast cancer incidence. We found a significant dose-response relationship between the cumulative activity of therapeutic RAI and breast cancer risk after a minimal latency time of 10 years, with no evidence of departure from linearity. The estimated excess relative risk was 0.5% per 10 mCi. This result was driven by high cumulative activity RAI (200- >400 mCi); no significant increased risk was found for lower exposures (treatment of hyperthyroidism typically involves activities around 10 mCi). When applied to typical RAI exposure received for hyperthyroidism treatment, the estimated relative risk translates into 0.4 excess breast cancer cases after 10,000 person-years since exposure.

In conclusion, this thesis showed modest associations between thyroid dysfunction and breast cancer risk, which could not be explained by RAI exposure. Rather, the intertwined roles of hyperthyroidism etiology and blood levels of thyroid hormones and estrogens on breast cancer risk should be better characterized. In addition, efforts are still needed to further address potential subpopulations at higher risk (e.g. postmenopause).

université PARIS-SACLAY | ÉCOLE DOCTORALE Santé Publique (EDSP)

RESUME SUBSTENTIEL

Titre : Association entre la dysfonction thyroïdienne et le risque de cancer du sein chez la femme adulte

Mots clés : Dysfonction thyroïdienne, hyperthyroïdie, hypothyroïdie, cancer du sein, iode radioactive, cohorte

La dysfonction thyroïdienne désigne les conditions pathologiques qui se manifestent par une carence (hypothyroïdie) ou un excès (hyperthyroïdie) d'hormones thyroïdiennes synthétisées et sécrétées par la glande thyroïde. L'hyperthyroïdie et l'hypothyroïdie sont des affections fréquentes chez les femmes, qui impliquent souvent une prise en charge à vie et éventuellement diverses complications. Les conséquences à long terme de la dysfonction thyroïdienne, notamment le risque de développer un cancer du sein, sont préoccupantes, mais restent toujours insuffisamment étudiées. Bien que les études expérimentales aient suggéré une association possible entre la dysfonction thyroïdienne et le cancer du sein, les études épidémiologiques ont rapporté des résultats contradictoires, avec des débats continus sur l'effet des niveaux anormaux d'hormones thyroïdiennes et des traitements de la dysfonction thyroïdienne (par exemple l'iode radioactif - IRA). Ces divergences pourraient être dues à des différences dans la conception des études, l'étiologie de la dysfonction thyroïdienne, l'inclusion des cas de cancer prévalents et la possibilité d'une causalité inverse. En outre, la plupart des études ne contenaient pas d'informations détaillées sur les traitements des dysfonctionnements thyroïdiens, qui variaient en fonction de la gravité et des étiologies des dysfonctionnements thyroïdiens. Par conséquent, ce projet de thèse visait à évaluer l'association entre le risque de cancer du sein chez la femme et la dysfonction thyroïdienne, en tenant compte des traitements de la dysfonction thyroïdienne, des comorbidités et des facteurs de risque du cancer du sein.

Le projet était principalement basé sur la cohorte UK Biobank (UKB) et sur les données que nous avons extraites d'une revue systématique et d'une méta-analyse sur le risque de cancer associé à la dysfonction thyroïdienne dans la littérature scientifique. L'UKB est une cohorte basée sur la population, qui comprenait 273.375 femmes âgées de 40 à 69 ans à l'inclusion entre

2006 et 2010 à travers le Royaume-Uni. Des données détaillées sur les antécédents médicaux personnels et familiaux, les médicaments, le mode de vie, les caractéristiques reproductives et socio-économiques ont été recueillies lors de la visite d'évaluation initiale. La cohorte UKB a été reliée aux bases de données régionales et nationales de patients hospitalisés (disponibilité des données entre 1981 et 1998 selon les régions), aux registres du cancer (depuis 1957 à 1971 selon les régions) et aux registres des décès (depuis 2006). Dans le cadre du projet de thèse, nous avons inclus dans nos analyses finales 239.436 femmes qui n'avaient aucun antécédent de cancer (à l'exception du cancer de la peau non mélanome), aucune mastectomie avant l'inclusion et qui avaient au moins un an de suivi. Nous avons utilisé des modèles de Cox pour estimer les rapports de risque (HR) de l'incidence du cancer du sein associés au diagnostic et aux traitements de la dysfonction thyroïdienne (médicaments antithyroïdiens, IRA ou chirurgie), et nous avons examiné les facteurs de confusion et les médiateurs potentiels, i.e. les comorbidités et les facteurs de risque du cancer du sein. Dans la cohorte UKB, 3.227 (1,3%) et 20.762 (8,7%) femmes souffraient d'hyper- et d'hypothyroïdie avant l'inclusion. Au cours d'une période de suivi médiane de 7 ans, 5.326 cas incidents de cancer du sein ont été diagnostiqués. Après avoir pris en compte des facteurs de confusion importants, nous n'avons trouvé aucune association significative entre le risque de cancer du sein et l'hyper- (HR = 0,93, intervalle de confiance (IC) à 95%: 0,84-1,02, 79 cas) ou l'hypothyroïdie (HR = 0,93, IC95%: 0,84-1,02, 442 cas). Cependant, le risque de cancer du sein était 38% plus élevé chez les femmes traitées pour une hyperthyroïdie que chez les femmes ne présentant pas de dysfonctionnement thyroïdien (IC95%: 1,03-1,86, 44 cas), quelle que soit la modalité de traitement. Aucune augmentation du risque n'a été observée chez les femmes hyperthyroïdiennes ne disposant pas d'informations sur les traitements (HR=0,84, 95%CI: 0,60-1,17, 35 cas). Ces résultats suggèrent un effet de la gravité de l'hyperthyroïdie (c'est-à-dire des taux d'hormones thyroïdiennes plus élevés) et/ou de son étiologie (goitre nodulaire toxique ou récidive de la maladie de Basedow) sur l'incidence du cancer du sein.

En combinant ces résultats avec toutes les preuves actuellement disponibles dans la littérature (sur Pubmed/Medline et la Cochrane Library depuis le début jusqu'au 29 juillet 2021), 14 études (11 études de cohorte et 3 études cas-témoins) ont été incluses, dont 13 ont contribué à la méta-analyse. La prévalence de l'hyperthyroïdie et de l'hypothyroïdie variait respectivement de 0,3% à 2,5% et de 0,6% à 14,7% dans les études de cohorte (âge moyen lors de l'évaluation de la dysfonction thyroïdienne: 40 à 64 ans). Dans l'ensemble, neuf études (64%) ont été considérées

comme présentant un risque de biais modéré à faible. En utilisant les modèles à effet aléatoire de DerSimonian et de Laird, nous avons estimé un rapport de risque global de 1,15 pour l'hyperthyroïdie (IC95%: 1,04-1,38, 890 cas) et de 0,86 pour l'hypothyroïdie (IC95% 0,75-0,98, 2 427 cas) (traitée ou non), respectivement, par rapport à l'absence de dysfonctionnement thyroïdien. Peu d'études se sont penchées sur le risque de cancer du sein associé aux modalités de traitement de l'hyperthyroïdie (par exemple, IRA) et la différence par les différentes estimations de risque regroupées provenant de différents sous-groupes de traitement (IRA uniquement, femmes non traitées, traitements divers/non signalés) n'était pas statistiquement significative (p-hétérogénéité=0,44).

Tant dans la cohorte UKB que dans notre méta-analyse, les estimations du risque variaient en fonction du statut ménopausique et de l'âge à la ménopause. Dans la méta-analyse, le risque de cancer du sein était significativement réduit chez les femmes préménopausées atteintes d'hypothyroïdie (rapport de risque chez les femmes ménopausées = 0,69, IC95% 0,53-0,89, chez les femmes préménopausées = 0,92, IC95% 0,80-0,97, p-hétérogénéité=0,03), et augmentait, bien que de manière non significative, chez les femmes ménopausées souffrant d'hyperthyroïdie (rapport de risque chez les femmes ménopausées = 1,12, IC95% 0,97-1,29, chez les femmes préménopausées = 0,87, IC95% 0,59-1,30, p-hétérogénéité=0,24). Dans la cohorte UKB, nous avons constaté que chez les femmes qui ont connu la ménopause après l'âge de 51 ans (l'âge médian de la ménopause chez les participantes de la cohorte UKB), le risque plus faible de cancer du sein associé à l'hypothyroïdie a disparu (HR=1,10, IC95% 0,93-1,30) et le risque plus élevé associé à l'hyperthyroïdie traitée a augmenté de manière significative (HR=2,07, IC95% 1,33-3,22). Nos résultats suggèrent donc de manière cohérente que l'effet des hormones thyroïdiennes sur le risque de cancer du sein pourrait se renforcer chez les femmes ménopausées, en particulier celles qui ont connu une ménopause tardive.

Dans la cohorte UKB, nous n'avons pas trouvé d'autres effets confondants ou modificateurs significatifs liés à d'autres facteurs reproductifs, à des comorbidités (obésité, hypertension, diabète de type 2 et maladies auto-immunes) et à des facteurs liés à la santé (par exemple, l'activité physique). Nos analyses n'ont pas non plus varié en tenant compte de l'année civile, de l'adhésion aux recommandations pour le dépistage du cancer du sein et du col de l'utérus, et de l'indice de privation de Towsend, ce qui suggère que le biais de surveillance n'était probablement pas un facteur explicatif principal de nos résultats dans la cohorte UKB. Les

analyses de sensibilité ont également montré que la causalité inverse n'était pas non plus un facteur principal expliquant nos résultats.

En raison des limites des données disponibles dans la cohorte, nous n'avons pas été en mesure de rendre compte de la relation dose-réponse entre le risque de cancer du sein et le traitement cumulatif par IRA. Bien que des niveaux de dose différents soient généralement utilisés pour le traitement de l'hyperthyroïdie (~10-15 mCi pour la maladie de Basedow, ~10-20 mCi pour le goitre nodulaire toxique) et le traitement du cancer de la thyroïde (~100-≤200 mCi), nous avons émis l'hypothèse que la courbe dose-réponse estimée chez les survivantes du cancer de la thyroïde pouvait être extrapolée aux femmes hyperthyroïdiennes. Les analyses ont ensuite été étendues à une cohorte européenne groupée de survivants du cancer de la thyroïde traités en France, en Italie et en Suède en 1934-2005 et ayant survécu 2 ans sans malignité après leur premier diagnostic de cancer. Les informations sur les patients, y compris les détails sur la date d'administration de l'IRA et les activités, ont été obtenues à partir des dossiers médicaux des hôpitaux. Les cancers du sein ultérieurs ont été identifiés grâce aux dossiers médicaux et/ou aux registres nationaux. Sur les 8.475 femmes incluses dans les analyses primaires (âge moyen au moment du diagnostic: 45 ans, intervalle 2-90 ans), 335 cas de cancer du sein ont été signalés au cours d'une période de suivi médiane de 12,7 ans (intervalle 2-67 ans) depuis le diagnostic. Nous avons trouvé une relation dose-réponse significative entre l'activité cumulée de l'IRA thérapeutique et le risque de cancer du sein après un temps de latence minimal de 10 ans, sans preuve d'écart par rapport à la linéarité. L'excès de risque relatif (ERR) estimé était de 1,7% par 10 mCi (IC95%: 0,2% à 3,8%), correspondant à un ERR par 10 mGy de 0,5% (IC95%: 0 à 1,4%). Ce résultat est dû à une activité cumulative élevée de l'IRA (200- >400 mCi), et le risque le plus élevé a été observé chez les femmes qui ont reçu une activité cumulative de l'IRA de ≥400 mCi (RR=2,41, 95%CI 1,13-3,52). Aucune augmentation significative du risque n'a été constatée pour les expositions plus faibles. Appliqué à l'exposition typique à l'IRA reçue pour le traitement de l'hyperthyroïdie (10 mCi), le risque relatif estimé se traduit par 0,4 cas de cancer du sein en excès après 10 000 années-personnes depuis l'exposition. Nous n'avons pas trouvé d'effet modificateur significatif de l'âge/année au moment du diagnostic du cancer de la thyroïde, du temps de suivi depuis le diagnostic, de l'utilisation de la radiothérapie externe. Ces résultats nuls pourraient être dus au nombre limité de cas, et au fait que la plupart des femmes ont été diagnostiquées à l'âge adulte, et doivent être interprétés avec prudence.

Notre projet de thèse présente des atouts majeurs, notamment deux cohortes avec une grande taille de population. L'UKB présente un niveau élevé d'exhaustivité du suivi, une vérification confirmée des résultats et des informations détaillées sur un large éventail de facteurs de confusion potentiels. La cohorte européenne regroupée a une longue période de suivi et comprend des informations détaillées sur les dates d'administration et les activités du traitement par IRA. Nous reconnaissons plusieurs limites. Les détails sur le stade du cancer, le grade et le statut des récepteurs n'étaient pas disponibles dans les deux cohortes. Nous ne disposions pas d'informations sur les mesures de laboratoire des hormones thyroïdiennes, ni sur l'étiologie de la dysfonction thyroïdienne, ni d'informations longitudinales détaillées au cours du suivi sur l'état de la dysfonction thyroïdienne. La population étudiée n'était pas constituée de femmes souffrant d'hyperthyroïdie, mais de survivantes du cancer de la thyroïde. Le manque d'informations sur les facteurs de confusion pertinents, tels que l'obésité et les facteurs hormonaux, impose la prudence dans l'interprétation des résultats.

En conclusion, cette thèse a montré des associations modestes entre la dysfonction thyroïdienne et le risque de cancer du sein. Nos résultats soutiennent l'hypothèse selon laquelle des taux élevés d'hormones thyroïdiennes pourraient jouer un rôle clé dans le développement du cancer du sein chez la femme, mais n'éliminent pas un rôle potentiel de l'IRA. Cependant, le risque potentiel associé à l'IRA était susceptible de se produire après un long temps de latence. Pour mieux aborder l'interaction entre la gravité de l'hyperthyroïdie, les étiologies et les traitements, nous avons proposé un cadre causal avec un graphique acyclique dirigé détaillé qui présente ces associations complexes pour les recherches futures. En outre, les rôles entrelacés de l'étiologie de l'hyperthyroïdie et des taux sanguins d'hormones thyroïdiennes et d'œstrogènes sur le risque de cancer du sein devraient être mieux caractérisés. En outre, des efforts sont encore nécessaires pour étudier plus en détail les sous-populations potentielles à plus haut risque (par exemple, la post-ménopause).

université PARIS-SACLAY | ÉCOLE DOCTORALE Santé Publique (EDSP)

PUBLICATIONS DURING THE THESIS

Published

1. Tran TVT, Kitahara CM, de Vathaire F, Boutron-Ruault MC, Journy N. Thyroid dysfunction and cancer incidence: a systematic review and meta-analysis. Endocr Relat Cancer. 2020;27(4):245-59.

2. Tran TVT, Maringe C, Benitez Majano S, Rachet B, Boutron-Ruault M-C, Journy N. Thyroid dysfunction and breast cancer risk among women in the UK Biobank cohort. Cancer Med.

In preparation

Tran TVT, Rubino C, Allodji R, Andruccioli M, Bardet S, Corone C, Diallo I, Dottorini M, Hall P, Henry-Amar M, Larmart S, Le Thai F, Lönn S, Ricard M, Schvart C, Schlumberger M, Schlumberger M, Journy N, De Vathaire F. Breast cancer risk among thyroid cancer survivors and the role of I-131 treatment.

Oral presentation

International Society for Radiation Epidemiology and Dosimetry (ISoRED) webinar, July 6, 2021 Tran TVT, Rubino C, Allodji R, Andruccioli M, Bardet S, Corone C, Diallo I, Dottorini M, Hall P, Henry-Amar M, Larmart S, Le Thai F, Lönn S, Ricard M, Schvart C, Schlumberger M, Schlumberger M, Journy N, De Vathaire F. Breast cancer risk among thyroid cancer survivors and the role of I-131 treatment.

Highlighted poster presentation

90th Annual Meeting of the American Thyroid Association, October 2, 2021, Tran TVT, Rubino C, Allodji R, Andruccioli M, Bardet S, Corone C, Diallo I, Dottorini M, Hall P, Henry-Amar M, Larmart S, Le Thai F, Lönn S, Ricard M, Schvart C, Schlumberger M, Schlumberger M, Journy N, De Vathaire F. Breast cancer risk among thyroid cancer survivors and the role of I-131 treatment.

Research supervision

Afi Mawulawoe Sylvie HENYOH: Master 2 internship (March-September 2021), University Paris-Saclay: Disease patterns and the association with breast cancer risk among women in the UK Biobank cohort

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

AER: Absolute excess risk

ATDs: Anti-thyroid drugs

BMI: Body mass index

DAG: Directed Acyclic Graphs

DIT: Diiodotyrosine

ER: Estrogen receptor

ERR: Excess relative risk

HR: Hazard ratio

ICD: International Classification of Diseases

IPW: Inverse probability weighting

MHT: Menopausal hormone therapy

MIT: Monoiodotyrosine

NICE: National Institue for Health and Care Excellence

NIS: Sodium–iodide symporter

OPCS: Classification of Interventions and Procedures

RAI: Radioactive iodine

RR: Relative risk

T3: Triiodothyronine

T4: Thyroxine

Tg: Thyroglobulin

THRT: Thyroid hormone replacement therapy

TPO: Thyroid peroxidase

TRH: Thyrotropin-releasing hormone

TSH: Thyroid stimulating hormone

UKB: UK Biobank

Chapter I Introduction

I.1 Thyroid dysfunction and management

I.1.1 Thyroid gland, thyroid hormones, and thyroid dysfunction

I.1.1.1 Thyroid gland

The thyroid gland is the largest endocrine gland in the human body, which is located anteriorly in the lower neck, extending from the level of the fifth cervical vertebra down to the first thoracic (Figure 1). It consists of two lobes joined by a thin band of tissue, the isthmus. The tissue of the thyroid gland is composed mostly of thyroid follicles, with a central cavity called colloid surrounded by follicular epithelial cells. The colloid is the center of thyroid hormone synthesis, thyroxine (T4) and triiodothyronine (T3) (1).

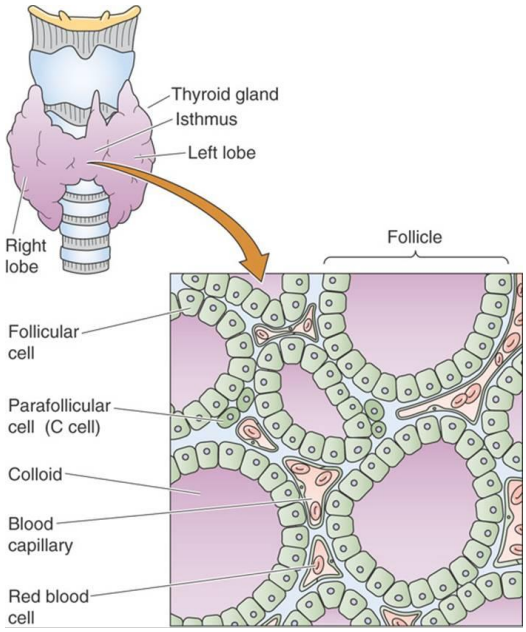


Figure 1 Thyroid gland anatomy.

Reprinted from Williams Textbook of Endocrinology, Melmed S, 2015, Elsevier Health Sciences (2)

I.1.1.2 Thyroid hormones synthesis, effects, and regulation

When the hypothalamus releases thyrotropin-releasing hormone (TRH), it stimulates the pituitary gland to release thyroid stimulating hormone (TSH). TSH activates the thyroid gland activity by binding the TSH receptors which are present in the plasma membrane of the thyroid

follicular epithelial cells, and are responsible to regulate iodide uptake and the expression of thyroid-specific proteins, such as thyroid peroxidase (TPO) , thyroglobulin (Tg) , and the sodium–iodide symporter (NIS) (1).

Iodide (I^-) from the bloodstream is actively transported into the thyroid follicular cells by the NIS, oxidized by TPO to form iodine (I_2), which goes into the colloid. In the colloid, TPO further catalyzes the iodination, which attaches one or two iodine to Tg, forming two intermediates, monoiodotyrosine (MIT) and diiodotyrosine (DIT). Further iodination couples one MIT with one DIT and two DITs together, resulting in the production of T3 and T4, respectively, which remain in the Tg chain in the colloid. When the thyroid hormone is needed, these Tg-hormone combinations go back into the follicular epithelial cells and are hydrolyzed to release free T3 and T4 which eventually enter the circulation. In the bloodstream, most thyroid hormones are bound to transport proteins, and only a small proportion is free and biologically active (1) (Figure 2).

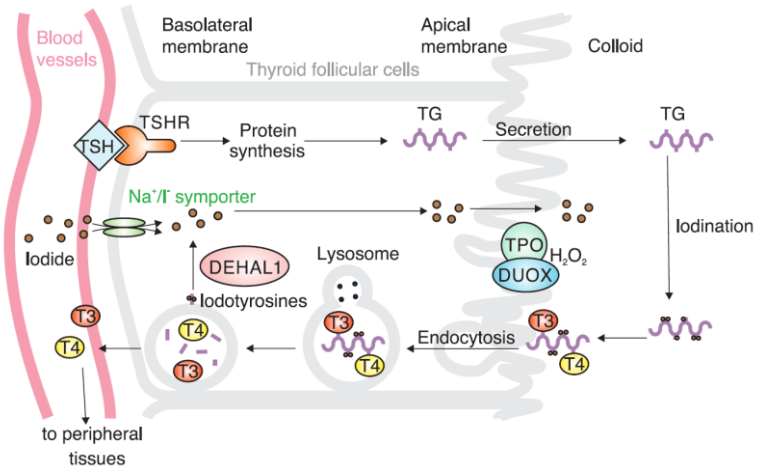


Figure 2 Thyroid hormone synthesis.

Reprinted from Coscia F et al. 2020 (3)

After thyroid hormones enter the target cells by passive transport, the deiodinase enzymes convert T4 into the more active form T3. The effects of thyroid hormone are classified into two main mechanisms: (1) genomic mechanisms, involving nucleus uptake of T3, the binding to thyroid hormone receptors and the subsequent regulation of specific thyroid hormone-responsive sequences in promoters of target genes, which induces regulating transcription; and (2) non-genomic mechanisms initiated at the plasma membrane that regulates downstream gene expression, primarily via integrin αvβ3 (4). Thyroid hormones exert their effects on almost

every organ and metabolic pathway. The physiological effects of thyroid hormones are summarized in Table 1.

Thyroid hormone synthesis is regulated by a negative feedback loop called the hypothalamic-pituitary-thyroid axis: when the serum thyroid hormone (T3, T4) concentrations increase above a certain threshold, the hypothalamus is signaled to stop secreting TRH, inducing the stop of TSH secretion of the pituitary gland. Without the stimulation of TSH, the thyroid gland stops producing thyroid hormones. When the serum thyroid hormone concentrations decrease below the threshold, the negative feedback is relieved, TRH secretion starts again, leading to TSH secretion (1).

In adults, thyroid hormone synthesis and regulation can be affected by other factors such as deficient or excessive iodine intake, pregnancy, aging, fasting, severe illness, and several hormones, e.g. glucocorticoids hormones, estrogen, growth hormone (1).

Table 1 Physiological effects of thyroid hormones.

Response	Comment
Fetal development	The thyroid and anterior pituitary TSH systems begin to function in the human fetus at ~11 weeks. The fetus does not receive much T3 + T4 from the mother.
Oxygen consumption, heat production	T3 increases O_2 consumption and heat production by stimulation of Na^+, K^+ ATPase in all tissues except brain, spleen, testis, and ovary.
Cardiovascular effects	T3 increases gene transcription of myosin heavy chain α and Ca^{2+} ATPase and mediates inotropic and chronotropic effects on the heart, which both increase cardiac output and heart rate in hyperthyroidism.
Sympathetic effects	T3 increases the number of β-adrenergic receptors in heart muscle, skeletal muscle, adipose tissue, and lymphocytes.
Skeletal actions	Stimulate increased bone turnover (resorption > formation).
Carbohydrate and lipid metabolism	Hyperthyroidism increases hepatic gluconeogenesis and glycogenolysis.
Gastrointestinal effects	T3 stimulates gut motility.

Reprinted from the Hormones (Second Edition), Norman AW, 1997, San Diego: Academic Press (5)

I.1.1.3 Thyroid dysfunction

Thyroid dysfunction refers to pathological conditions, which manifest as a deficiency (hypothyroidism) or an excess (hyperthyroidism) of thyroid hormones synthesized and secreted by the thyroid gland. Thyroid dysfunction can be overt or subclinical, which is characterized by blood tests: subclinical thyroid dysfunction is defined as normal serum concentrations of free T4 and T3, but low or undetectable serum concentrations of TSH (subclinical hyperthyroidism) or high serum TSH concentrations (subclinical hypothyroidism). Overt hyperthyroidism occurs where serum TSH concentration is low, and thyroid hormones concentration is above the reference range. Overt hypothyroidism occurs when serum TSH concentration is high, and thyroid hormones concentrations are below the reference range (6-8) (Table 2).

Table 2 Thyroid dysfunction categorization based on thyroid hormone levels

TSH levels / FT4/FT3 levels	Below normal range	Above normal range
Above normal range		Overt hypothyroidism
Normal range	Subclinical hyperthyroidism	Subclinical hypothyroidism
Below normal range	Overt hyperthyroidism	

What is the reference range for TSH and thyroid hormone concentration?

The reference ranges for serum TSH and thyroid hormone concentrations are statistically defined as between the 2.5th and 97.5th percentile in a reference disease-free population. Therefore, the reference ranges can vary with age, sex, geographic regions, and ethnicity, and do not consider symptoms or risk of adverse events or disease. Often, 0.4-4 mIU/l is considered as the reference range for TSH in the current guidelines, but the applied reference ranges for both TSH and thyroid function have been a matter of debate recently (6, 9, 10)

I.1.2 Hyperthyroidism

I.1.2.1 Epidemiology

The prevalence and incidence of hyperthyroidism vary considerably according to geographical regions, diagnostic thresholds, assay sensitivity, and iodine intake (11) (Figure 3). In iodine-sufficient regions, the prevalence of overt and subclinical hyperthyroidism range from 0.5 to 0.8% and 0.7 to 2.9%, respectively (12, 13). The disease is most frequent in white people (7) and is more common in women than men (14), with a prevalence of 1.4% and 0.3% respectively, in Europe (12). The predominance of hyperthyroidism in women is also reflected

in the sex-specific incidence, which was estimated at 82 and 16 per 100,000 person-years for women and men, respectively, in Europe (12). The incidence of hyperthyroidism increases with age and is higher in iodine-deficient regions, probably because mild-to-moderate iodine deficiency increases the rates of hyperthyroidism due to toxic goiter (11), and the rate tends to decrease after the introduction of universal salt iodization programs (7). Other risk factors, e.g., smoking status, alcohol consumption, presence of other autoimmune conditions, syndromic conditions, and exposure to some therapeutic drugs, also influence thyroid disease epidemiology (7).

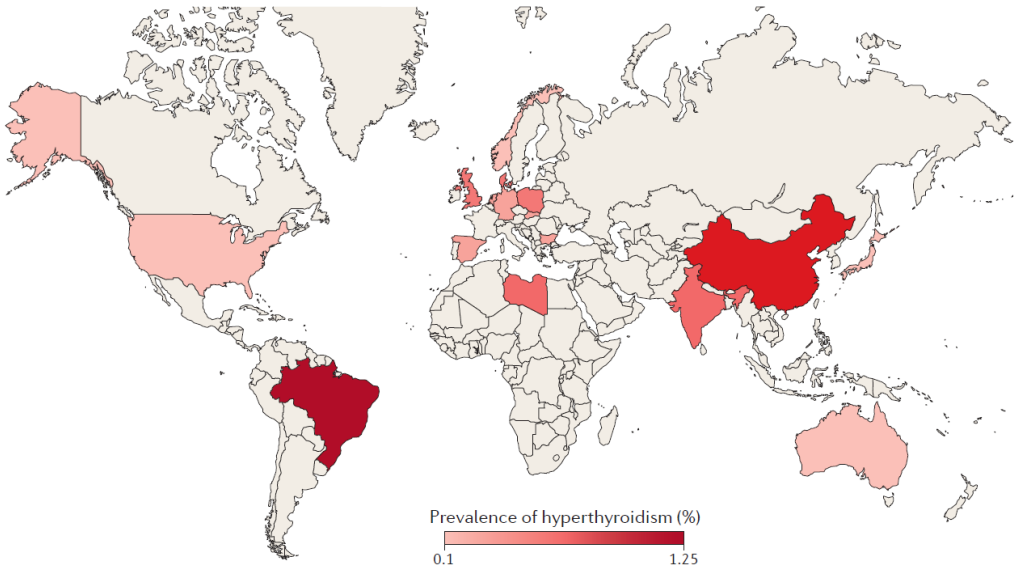


Figure 3 Map of overt hyperthyroidism prevalence.

Selective populations used when representative data not available. World map showing the global prevalence of hyperthyroidism based on epidemiological samples. The deeper the shade of red, the higher the prevalence of hyperthyroidism. Countries in white represent no data available. Reprinted from Taylor P et al. 2018 (11).

I.1.2.2 Etiology

The most common causes of hyperthyroidism are Graves' disease, toxic multinodular goiter, and thyroid toxic adenoma. Less common causes are thyroiditis, excess iodine exposure, thyrotropin-induced thyrotoxicosis, and trophoblastic tumors (7, 15, 16).

Graves' disease is a thyroid autoimmune condition, which stimulates the immune system to produce an antibody which mimics TSH function and stimulates the thyroid gland to produce

an excess amount of thyroid hormones. Toxic multinodular goiter and thyroid toxic adenoma refer to a thyroid gland that contains autonomously functioning thyroid nodules, which secret thyroid hormones independently of the signals from TSH.

In iodine-sufficient regions, Graves' disease is the most common cause of hyperthyroidism (70-80%) (11). In contrast, in areas with iodine deficiency, toxic multinodular goiter and solitary toxic adenoma are more frequently hyperthyroidism causes, particularly among elderly people.

I.1.2.3 Clinical manifestations, complications, and associated morbidities

I.1.2.3.1 Signs and symptoms

Common symptoms of hyperthyroidism include weight loss, palpitations, breathlessness, tremor, tiredness, heat intolerance, excessive sweating, increased bowel action, anxiety, nervousness, muscle weakness, menstrual disturbances, and loss of libido (16) (Table 3). There are also signs and symptoms specific to the underlying causes of hyperthyroidism: ophthalmopathy, thyroid dermopathy, and thyroid acropachy in Graves' disease; globus sensation, dysphagia, or orthopnoea due to oesophageal or tracheal compression in nodular goiter; and anterior

Table 3 Symptoms and signs of thyrotoxicosis.

	Symptoms	Signs
Central nervous system	Fatigue, nervousness, anxiety, hyperactivity, poor concentration	Hyperactivity
Hair	Thinning, hair loss	
Eyes (usually in Graves' disease)	Soreness, grittiness	Stare, eyelid retraction and lag, periorbital edema, conjunctival injection, ophthalmoplegia
Thyroid	Neck swelling	Goiter
Muscles	Weakness, tremor	Fine tremor, muscle wasting
Skin	Heat intolerance, increased perspiration	Warm, moist skin, increased perspiration
Cardiovascular system	Palpitation, shortness of breath	Tachycardia, atrial arrhythmia, systolic hypertension, high output failure
Gastrointestinal system	Increased appetite, weight loss	Weight loss
Peripheral nervous system		Hyperreflexia
Reproductive system		Oligomenorrhoea, decreased fertility (women); reduced libido (men)

Reprinted from Franklyn JA et al. 2012 (17)

neck pain in painful subacute thyroiditis (7). Older patients are more likely to have fewer and less pronounced signs and symptoms than younger patients, although they tend to develop more cardiovascular complications (18, 19). Clinical manifestations also vary depending on sex, comorbidities, duration of the disease, and causes.

I.1.2.3.2 Cardiovascular and metabolic diseases

Among pathological complications and long-term consequences of hyperthyroidism, the cardiovascular system is the most extensively investigated. Both overt and subclinical hyperthyroidism is associated with increased cardiovascular mortality, incidence of atrial fibrillation, embolic events and stroke, ischaemic heart disease, congestive cardiac failure, and changes in coagulation indicators (17, 20). Moreover, hyperthyroidism also has a role in the pathogenesis of pulmonary hypertension (20). Controlled hyperthyroidism with treatments can be able to reduce the risk of cardiovascular morbidity and mortality among individuals with the condition (6, 20).

Population-based longitudinal studies have assessed the risk for type 2 diabetes associated with hyperthyroidism among both adolescents and adults in a wide range of ages (21-23). They found that hyperthyroidism is associated with a 1.2-1.7-fold higher risk of type 2 diabetes, compared to euthyroidism.

I.1.2.3.3 Autoimmune diseases

Individuals with Graves' disease are more likely to have another concomitant autoimmune disorder than the general population (24, 25). Specifically, previous studies found a frequency of 9.7-17% of other autoimmune diseases in Graves' disease compared to 3.3-3.9% in healthy controls (25, 26). Common coexisting autoimmune diseases include rheumatoid arthritis, chronic autoimmune gastritis, vitiligo, polymyalgia rheumatica, celiac disease, type 1 diabetes, Sjogren disease, multiple sclerosis, systemic lupus erythematosus, sarcoidosis, alopecia, psoriatic arthritis, systemic sclerosis, and HCV-related cryoglobulinemia (24-26). Accordingly, previous studies have shown that patients with Graves' disease were at a significantly increased risk of other autoimmune diseases and vice versa (10, 26, 27).

I.1.2.3.4 Reproductive disorders

Hyperthyroidism might adversely affect both male and female reproductive function. Specifically, in males, hyperthyroidism might cause gynaecomastia (7) or induce abnormalities in sperm motility, whereas in females, hyperthyroidism causes menstrual disturbances and reduced fertility. These abnormalities improve or normalize when euthyroidism is restored (28).

I.1.2.4 Diagnosis

In presence of hyperthyroidism symptoms, hyperthyroidism diagnosis is initially based on measurement of serum TSH concentration because of its high sensitivity and specificity for detecting thyroid disorders. If the TSH concentration is below the lower limit of the reference range, serum free T4 and free or total T3 are often measured to ascertain whether hyperthyroidism is overt or subclinical. Methods to determine the cause of hyperthyroidism vary according to the doctor's preferences and include physical examination, radioiodine uptake or thyroid ultrasound, and measurement of serum TSH-receptor.

I.1.2.5 Management

Overt hyperthyroidism is often treated as soon as diagnosed while treatments are not recommended for subclinical hyperthyroidism, unless in case of ≥65 years of age and having very low serum TSH concentrations (<0.1 mU/l) (9). The goals of hyperthyroidism treatments are to control symptoms efficiently and to restore euthyroidism (7, 16). Three recognized treatment modalities for hyperthyroidism include: anti-thyroid drugs (ATDs), radioactive iodine (RAI), and surgery (thyroidectomy). Additionally, beta-blocker can also be used for symptom reliefs (7, 16).

I.1.2.5.1 Anti-thyroid drugs

The main mechanisms of ATDs are inhibition thyroid hormone synthesis, by competing with Tg to act as substrates for iodination by TPO, thereby decreasing numbers of MIT and DIT (1, 29). Three ATDs are commercially available, including methimazole, propylthiouracil, and carbimazole (16). The last two are common ATDs in the UK (30). ATDs can be prescribed for Graves' disease as the primary treatment, and for toxic nodular goiter and toxic adenoma as preliminary euthyroidism-rendering treatments before definitive treatments (surgery, RAI), or

as a long-term treatment when surgery and RAI are contraindicated or short life expectancy (7, 16). The definite contraindication of ATDs is previous major adverse reactions to ATDs (9). Normally, euthyroidism can be achieved after 4-8 weeks of ATDs usage. ATDs can still be prescribed up to 12-18 months, but prolonged usage for more than 18 months offers no advantage. The rate of relapse after discontinuation is relatively high (50%) and thyroid hormone concentrations should be measured every 4-6 weeks to detect early signs of relapse (7, 9, 16).

I.1.2.5.2 Radioactive iodine

RAI (iodine-131) is a beta and gamma radiation emitter absorbed mostly by the thyroid gland after oral ingestion, causing DNA damage and inducing thyroid cell death (1, 29). RAI can be prescribed as the primary treatment for Graves' disease, toxic multinodular goiter, and toxic adenoma. The treatment is contraindicated in case of pregnancy or planning pregnancy, lactation, active inflammatory Graves' ophthalmopathy, and inability to comply with radiation safety recommendations. RAI doses could be fixed or individually estimated using dosimetry (7, 16). When using fixed doses, 10–15 mCi is often the suggested dose for treating Graves' disease, and 10–20 mCi is suggested for toxic nodular goiter (9). Most patients treated with RAI subsequently develop hypothyroidism and have to take thyroid hormone replacement as a long-term treatment (7).

I.1.2.5.3 Thyroid surgery

Thyroid surgery, as known as thyroidectomy, is a surgical procedure in which all (total) or most (near total) of the thyroid gland is removed. Total or near total thyroidectomy can be indicated for Graves' disease with relapse, active Graves' ophthalmopathy, large goiters, low uptake of radioactive iodine, suspected or documented thyroid cancer (7, 16). Contrarily, thyroidectomy should be avoided in patients who have substantial comorbidity (e.g. cardiopulmonary disease, end-stage cancer) or who are in the first and third trimesters of pregnancy (31). To prepare for the surgery, patients need to be euthyroid, either with ATDs or other medications (e.g. potassium iodide, Lugol's iodine, oral cholecystographic) (7, 32). Total thyroidectomy will definitely cause hypothyroidism and up to 30-50% of patients having partial thyroidectomy will develop hypothyroidism. After surgery, patients need to take thyroid hormone replacement as a long-term treatment (7).

I.1.2.5.4 Treatment protocols:

ATDs, RAI, and surgery are all effective but do not individually offer an ultimate cure. Definitive management (RAI and surgery) is consistently suggested to cure toxic multinodular goiter and toxic adenoma, except contraindicated. Contrarily, the preference for treatment modalities for Graves' disease varies according to geographic regions, time periods, and patient preference (7, 32). In the US, RAI is often the preferred treatment for Graves' disease, while in Europe and Asia, ATDs are often the first-line treatment. In the UK, RAI is commonly used to treat severe cases of Graves' disease, and after a relapse or side effects from ATDs (32-34). However, in 2019, a new guideline of National Institue for Health and Care Excellence (NICE, UK) recommends RAI as the initial management for Graves' disease (35) (Figure 4).

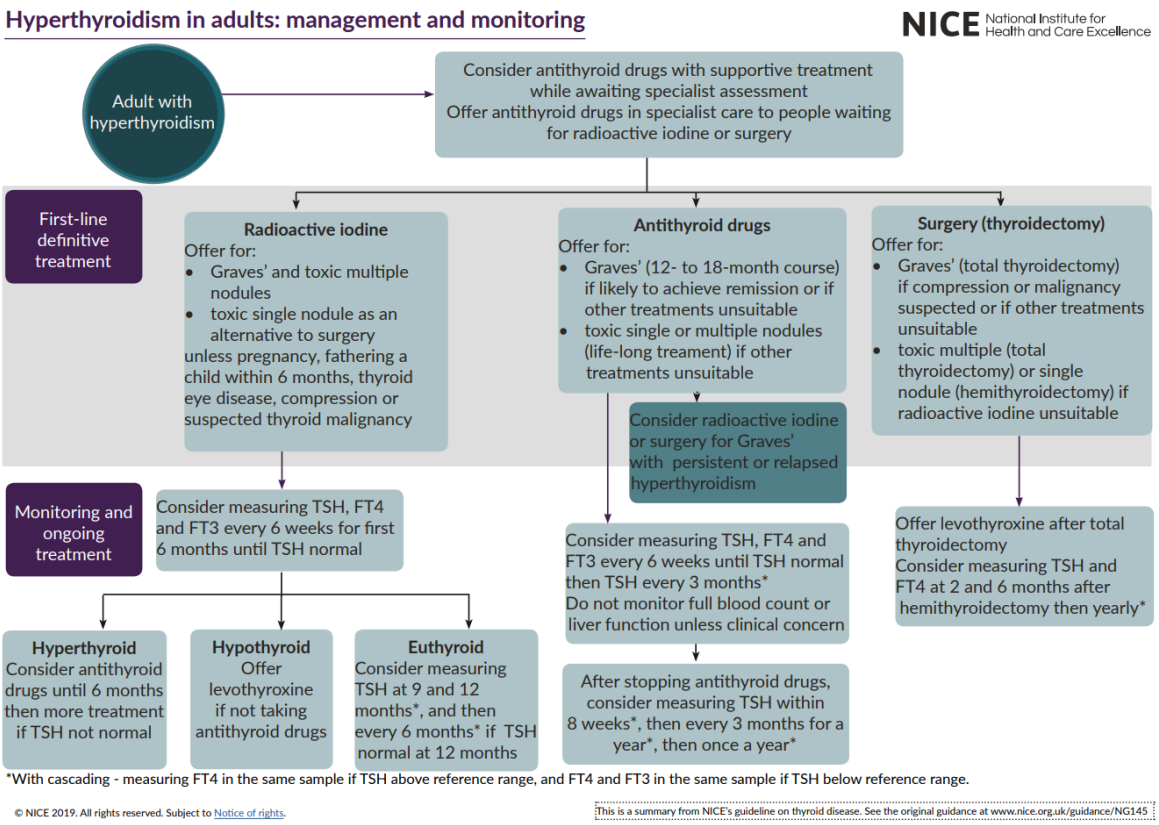


Figure 4 Guideline for hyperthyroidism management in the UK

Reprinted from: www.nice.org.uk/guidance/ng145/resources/visual-summary-pdf-6965793901 (according to the NICE guideline published in 2019 (35))

I.1.3 Hypothyroidism

I.1.3.1 Epidemiology

The prevalence of hypothyroidism varies substantially worldwide and is more common in populations with a relatively high iodine intake or severe iodine deficiency (Figure 5) (11). In iodine-sufficient regions as Europe and the US, it is estimated that the prevalence ranges from 3.0 to 4.6% (12, 13), in which subclinical hypothyroidism makes up most hypothyroidism cases (12). Such prevalence is increased in women, elderly populations, and in white people than other races (6, 11, 14). In Europe, the incidence rate of hypothyroidism is 370 and 72 per 100000 person-years for women and men, respectively (12).

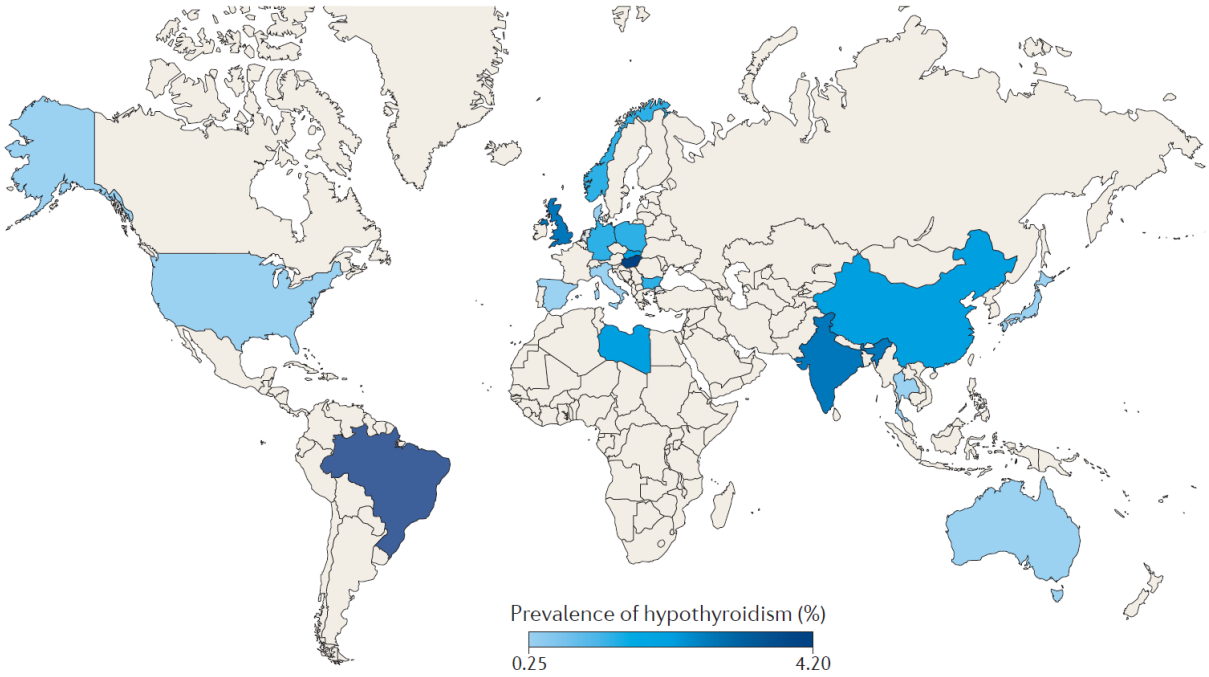


Figure 5 Map of overt hypothyroidism prevalence

Selective populations used when representative data not available. World map showing the global prevalence of hypothyroidism based on epidemiological samples. The deeper the shade of blue, the higher the prevalence of hyperthyroidism. Countries in white represent no data available. Reprinted from Taylor P et al. 2017 (11).

I.1.3.2 Etiology

Most hypothyroidism cases (99%) are primary hyperthyroidism (due to deficiency of thyroid hormones) (6). Iodine deficiency is frequently the cause of primary hypothyroidism worldwide.

However, in iodine-sufficient regions, primary hypothyroidism is most commonly caused by Hashimoto's disease – a thyroid autoimmune condition, which produces antibodies that destroy thyroid cells (1). Other causes include thyroid removal after thyroid surgery, irradiation with external radiation therapy or RAI, medications (e.g. amiodaron, lithium), and a variety of other less common causes (6, 36).

I.1.3.3 Clinical presentation, complications, and associated morbidity

I.1.3.3.1 Signs and symptoms

The symptoms for hypothyroidism diagnosis are often non-specific, and in many cases, hypothyroidism is asymptomatic (6, 36, 37). The most common symptoms of hypothyroidism include fatigue, lethargy, cold intolerance, weight gain, constipation, change in voice, and dry skin. Older patients are more likely to have fewer and less pronounced signs and symptoms than younger patients. Clinical manifestation also varies depending on sex, and duration of the disease (6) (Table 4).

I.1.3.3.2 Cardiovascular and metabolic diseases

Higher TSH concentrations, especially when >10 mIU/l, are associated with an increased risk of coronary heart disease and mortality, risk of heart failure, and stroke, particularly in younger individuals (6). Hypothyroidism diagnosis has also been associated with nonalcoholic fatty liver disease (6), obesity (38), compared to euthyroidism. Controlled hypothyroidism with treatments can be able to reduce the risk of cardiovascular morbidity and mortality among individuals with the condition (6, 20).

Population-based longitudinal studies have assessed the risk for type 2 diabetes associated with hypothyroidism among both adolescents and adults in a wide range of ages and showed that hypothyroidism is an independent risk factor for new onset diabetes, (22, 39-41).

I.1.3.3.3 Autoimmune diseases

Among individuals with Hashimoto's disease, the proportion of having another autoimmune disorder are higher than among the general population. Specifically, a large study has found a frequency of 14.3% in Hashimoto's disease (26). Common coexisting autoimmune diseases include rheumatoid arthritis, chronic autoimmune gastritis, vitiligo, polymyalgia rheumatica,

celiac disease, type 1 diabetes, Sjogren disease, multiple sclerosis, sarcoidosis, alopecia, Systemic lupus erythematosus, psoriatic arthritis, systemic sclerosis, and HCV-related cryoglobulinemia (24, 26). Patients with autoimmune thyroid diseases are at a significantly increased risk of additional autoimmune diseases (26, 27). Conversely, patients affected with the above mentioned autoimmune disorders are more frequently affected by autoimmune thyroid diseases (10, 27).

Table 4 Common clinical presentation and implications of hypothyroidism.

	Presentation	Signs and implications
General metabolism	Weight gain, cold intolerance, fatigue	Increase in body-mass index, low metabolic rate
Cardiovascular	Fatigue on exertion, shortness of breath	Dyslipidaemia, bradycardia, hypertension
Neurosensory	Hoarseness of voice, decreased taste, vision, or hearing	Neuropathy, cochlear dysfunction, decreased olfactory and gustatory sensitivity
Neurological and psychiatric	Impaired memory, paresthesia, mood impairment	Impaired cognitive function, delayed relaxation of tendon reflexes
Gastrointestinal	Constipation	Reduced oesophageal motility
Endocrinological	Infertility and subfertility, menstrual disturbance, galactorrhoea	Goiter, glucose metabolism dysregulation, infertility, sexual dysfunction, increased prolactin
Musculoskeletal	Muscle weakness, muscle cramps, arthralgia	Creatine phosphokinase elevation
Hemostasis and hematological	Bleeding, fatigue	Mild anemia
Skin and hair	Dry skin, hair loss	Coarse skin
Electrolytes and kidney function	Deterioration of kidney function	Decreased estimated glomerular filtration rate

Adapted from Chaker L et al., 2017 (6)

I.1.3.3.4 Reproductive conditions

Hypothyroidism might adversely affect both male and female reproductive function. Specifically, in males, hypothyroidism might cause abnormalities in sperm morphology, whereas in females, hyper- and hypothyroidism cause menstrual disturbances and reduced fertility. These abnormalities improve or normalize when euthyroidism is restored (28). Maternal hypothyroidism can lead to serious obstetric complications, including an increased risk of miscarriage, placental abruption, and preterm delivery (8).

I.1.3.4 Diagnosis and management

When suspected, hypothyroidism diagnosis is initially based on serum TSH concentrations (Figure 6). If the TSH concentrations are above the high limit of the reference range, serum free T4 concentrations will be measured to ascertain whether hypothyroidism is overt or subclinical. To confirm the autoimmune cause of hypothyroidism, serum TPO antibody concentrations are often useful (6).

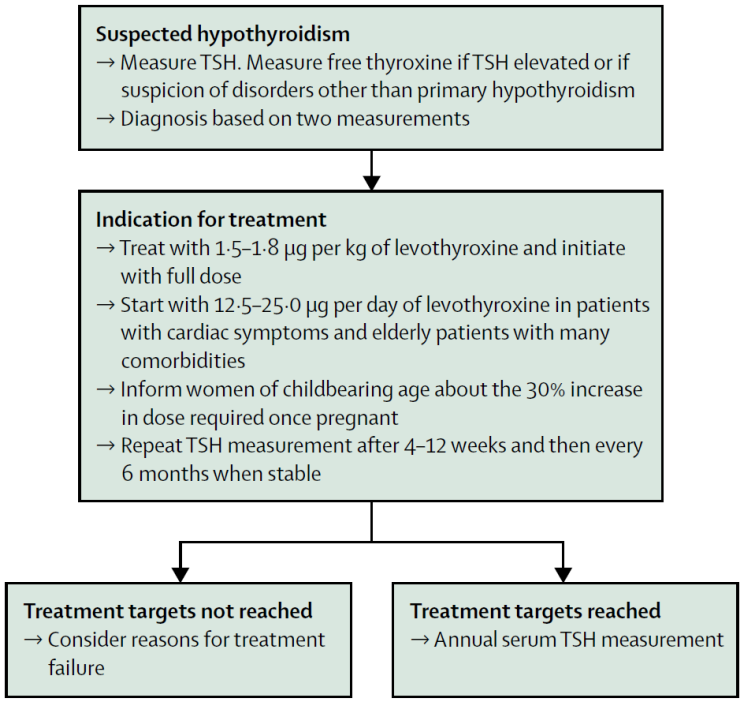


Figure 6 Diagnosis and treatment of primary hypothyroidism.

Reprinted from Chaker L et al. 2017 (6)

Levothyroxine in oral digestion is the treatment of choice for hypothyroidism (Figure 6). Treatment initiation often starts in presence of hypothyroidism symptoms and biochemical confirmation of overt hypothyroidism (6). In most cases, persistent subclinical hypothyroidism only undergoes periodic checks and is often untreated, unless in case of having very high serum TSH concentrations (≥7.0mU/l) (36). The goal of hypothyroidism treatment is to restore clinical and biochemical euthyroidism, to reduce the risk of cardiovascular diseases, and to avoid over- and under-treatment (37). After the initiation of therapy, serum TSH concentrations should be measured periodically, and adjustment of levothyroxine dosage should be made accordingly. Although the majority of hypothyroid adult patients on levothyroxine have a satisfactory response to the treatment, some still experience persistent symptoms. In some cases, the use of

combination therapy with both levothyroxine and liothyronine has been suggested but remains highly controversial (42, 43).

I.2 Thyroid dysfunction and risk of cancer

Thyroid dysfunction has been suggested to be related to cancer incidence and mortality. Several mechanisms have been proposed, such as enhancing tumor proliferation through thyroid hormone cell surface receptors, estrogen pathways, increasing angiogenesis, and gene expression regulation (44, 45). Moreover, as aforementioned, thyroid dysfunction is associated with the occurrence of obesity, diabetes mellitus, and cardiovascular diseases, which are either a breast cancer risk factor per se, or share common risk factors with breast cancer.

The association between thyroid dysfunction and cancer risk is not consistent in previous epidemiological studies. Several studies (46-49), but not all (50), have shown an increased overall cancer incidence associated with low TSH or high FT4 concentrations, or a diagnosis of hyperthyroidism. Studies on cancer mortality also showed controversial findings with elevated rates among individuals with hyperthyroidism/abnormally high thyroid hormone levels compared to euthyroid individuals, especially among those with toxic nodular goiters in some studies (51, 52), but also no (50) or even an inverse association (53) in others. The associations might vary according to site-specific cancers, and other important factors (e.g., thyroid dysfunction etiology, thyroid dysfunction treatments, age, sex, and reproductive factors) (51, 54, 55). For example, in a prospective study conducted on individuals with no prior thyroid dysfunction at baseline, high TSH and FT4 concentrations were associated with a higher cancer risk among individuals younger than 50 at inclusion, but a lower cancer risk among those aged 50 or more (56).

In conclusion, the current state of the literature highlights the need to conduct studies on site-specific cancer risk associated with thyroid dysfunction to obtain reliable risk estimates and to further understand the underlying causes. Up to now, most previous studies on site-specific cancers focus on thyroid and breast cancer risk. While previous studies consistently reported an increased risk of thyroid cancer for both hyper- and hypothyroidism (51, 54, 57, 58), epidemiological evidence on the association between breast cancer risk and thyroid dysfunction remains controversial.

I.3 Thyroid function and breast cancer incidence

The association between thyroid hormone status and breast cancer risk was first reported in 1896 when Beatson used thyroid extract as a potential treatment for breast cancer (59). Ever since, biological, clinical, and epidemiological studies have tried to enhance the understanding of the association, however, the role of thyroid dysfunction in the breast neoplasms process remains unclear. In this section, we present a summary of biological, clinical, and epidemiological studies of thyroid hormones and thyroid dysfunction on breast cancer risk, followed by a brief discussion of barriers and challenges for epidemiological studies and the problem statement.

I.3.1 Current state of the field

I.3.1.1 Thyroid hormones and breast cancer

Biological evidence

Thyroid hormones are able to exert their effects via both genomic and nongenomic pathways, the latter has been suggested to be involved in breast carcinogenesis by stimulating cell proliferation, apoptosis, angiogenesis, and migration via the integrin αvβ3 located in the cell membrane (Figure 7). Specifically, the integrin αvβ3 contains two binding domains for thyroid hormones:

(1) S1: S1 specifically recognizes T3 (but not T4) and activates the phosphatidylinositol 3-kinase/Akt/protein kinase B pathway. Binding to S1, T3 promotes the phosphorylation of FAK, an essential regulator of the actin cytoskeleton, thereby modulating cell adhesion and migration (60). T3 also directly increases aerobic glycolysis, a hallmark of cancer, which is known as the Warburg effect (60)

(2) S2: Both T3 and T4 are able to bind to S2, although T4 has a higher affinity. The binding thyroid hormones-S2 leads to the regulation of MAPK/ERK1/2, resulting in the proliferation of tumor cells and phosphorylating the estrogen receptor (ER) alpha (4), which demonstrated the crosstalk between thyroid hormones and estrogen. Previous studies have also shown that in human breast cell lines MCF-7 and T47D, cell proliferation is promoted in a dose-dependent relationship respective to T3 and T4 (61). T4 is also capable of supporting breast cancer cells

either with or without the presence of ER (44) and of having anti-apoptotic properties by stimulating gene expression of cancer cell defense (4, 62). Moreover, protein kinase D can also be activated by T4-binding to the thyroid receptors on αvβ3 in a pro-angiogenic pathway that is dependent on basic fibroblast growth factor (4).

Moreover, excessive or insufficient iodine intake, which plays a key role in thyroid hormone production, could also be a risk factor for breast cancer (63). Taken together, current experimental evidence supports a positive association between high levels of thyroid hormones and a higher risk of breast cancer.

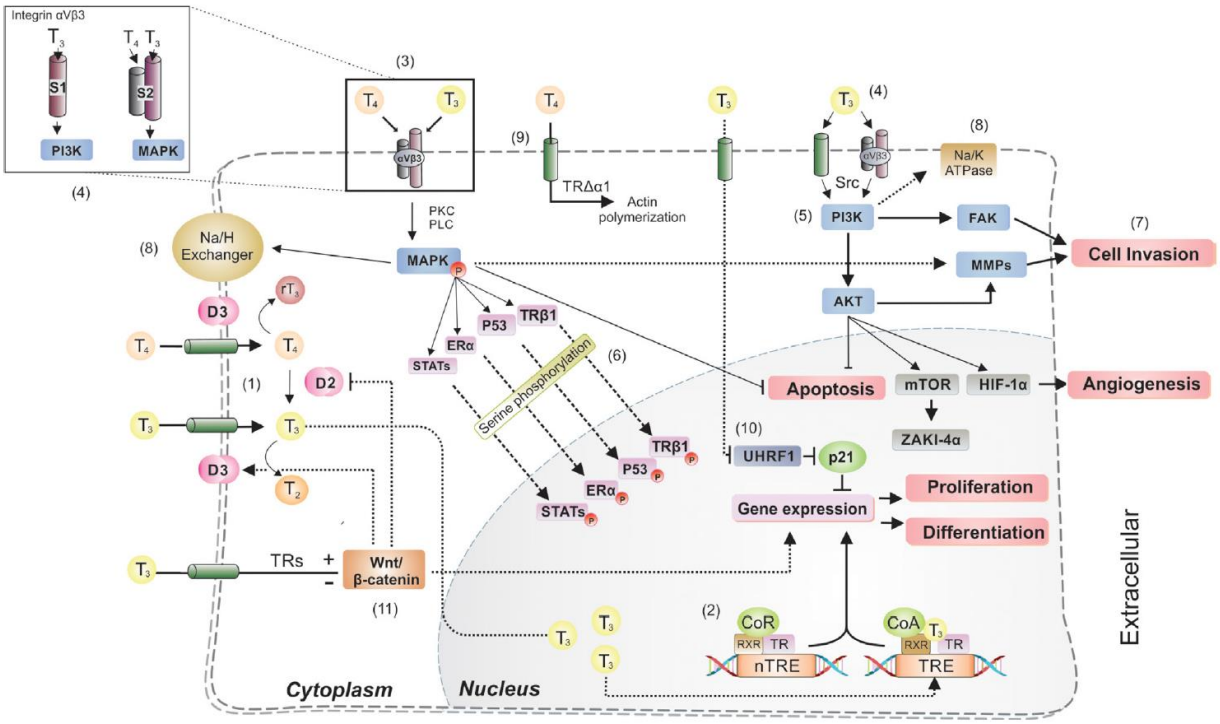


Figure 7 Proposed mechanism of genomic and nongenomic actions of THs in the neoplastic process

Reprinted from Goemann IM et al. 2017 (60)

Clinical and epidemiological evidence

In line with evidence from *in vitro* and *in vivo* studies, clinical and epidemiological have also suggested a relationship between thyroid hormones and breast cancer risk. Although most studies (46, 47, 64), but not all (65), found no association between serum TSH concentrations and breast cancer risk, thyroid hormone concentrations have been shown to be positively associated with the risk of breast cancer in a dose-response manner in women without thyroid

diseases at baseline, after adjusted for important confounders (64, 66). A prospective cohort study of women of 40 years of age or more with no thyroid medication at baseline has also reported that higher free T4 concentrations within the euthyroid range were positively associated with breast cancer risk (65). Moreover, the association between free T4 and breast cancer risk was mainly found in estrogen receptor-positive breast cancer ER+ and less aggressive cases (67). The findings were consistent in other smaller studies (46, 47, 68). A recent Mendelian randomization study (69) also showed that genetically predicted higher serum TSH concentrations and genetic predisposition to hypothyroidism were associated with a lower risk of breast cancer whereas genetically predicted serum free T4 concentrations and genetic predisposition to hyperthyroidism were associated with a higher risk of breast cancer.

I.3.1.2 Thyroid dysfunction and breast cancer risk

Although biological, clinical, and epidemiological evidence support the association between serum thyroid hormones concentrations and breast cancer risk, epidemiological studies have provided inconsistent findings on the association between hyper-, hypothyroidism, and breast cancer risk.

Up to the beginning of this thesis project in 2018, there are four meta-analyses published from 2002 to 2017 on the association between thyroid dysfunction and breast cancer risk. In the most recent meta-analysis in 2017, Fang et al. included 13 case-control studies, which reported no significant change in breast cancer risk associated with hyper- (10,766 cases, OR= 1.03, 95%CI 0.83–1.30), or hypothyroidism (12,106 cases, OR = 0.83, 95% CI 0.64–1.08) (70). These findings were in line with what had been reported by the three other meta-analyses (71-73). Fang et al also showed no risk change associated with thyroid hormone replacement therapy (THRT) (OR = 0.83, 95% CI 0.57–1.21). However, all previous meta-analyses highlighted a high level of heterogeneity across the included studies, and no information on important confounding and mediating factors, e.g., treatments, morbidities, reproductive factors, was reported. Inconsistent with the previous meta-analyses, two more recent large studies reported a reduced breast cancer risk associated with hypothyroidism (69, 74). Conversely, some studies (75-78), but not all (46, 74), showed a higher breast cancer risk among hyperthyroid women compared to those without thyroid dysfunction. This could be, at least partly, due to hyperthyroidism treatments, e.g. radioactive iodine (RAI). The breast is one of the most radiosensitive organs in females (66), and RAI therapy has been associated with an increased

breast cancer risk (64, 67). The association between hyperthyroidism and breast cancer risk thus could be an intertwined effect of the disease and the treatment.

I.3.2 Barriers and challenges

The discrepancy among epidemiological studies on the association between thyroid dysfunction and breast cancer risk might be explained by the differences in study design, thyroid dysfunction etiology, the inclusion of prevalent cancer cases, and the possibility of reverse causality. A gap in most studies is the lack of treatment information (ATDs, RAI, surgery, THRT), especially RAI dosage, which also reflects thyroid dysfunction etiology, and severity. Besides thyroid dysfunction, other important risk factors also influence breast cancer risk. The possible role of comorbidities and reproductive factors in the thyroid dysfunction-breast cancer risk association has also been poorly investigated. Yet thyroid dysfunction is strongly associated with multiple conditions such as diabetes (79, 80), obesity (38), hypertension (20, 81, 82), and depression (83), which in turn, are direct risk factors of - or share common risk factors with - breast cancer. The estrogen-like effects of thyroid dysfunction may also share pathways with other reproductive factors, suggesting a possible role of estrogens in the effect of thyroid dysfunction on breast cancer risk. To date, little is known about the role of treatments, comorbidities, and other breast cancer risk factors in the thyroid dysfunction-breast cancer risk associations which somewhat limits the interpretation of previous results as a causal relationship.

I.3.3 Problem statement

Since thyroid dysfunction is one of the most common chronic endocrine disorders in women, which often involves lifetime management and possibly various complications, long-term outcomes among individuals having these conditions are of great concern. Meanwhile, breast cancer risk is the most frequent female neoplasms whose biological mechanisms are suggested to be partly related to or modified by thyroid hormones and thyroid dysfunction treatments. It is important to further understand the risk of breast cancer among women with thyroid dysfunction, its underlying causes and to identify subpopulations which are at a higher risk of developing breast cancer after a diagnosis of hyper-, or hypothyroidism. The findings would help to inform clinicians, public health makers, and epidemiologists and to provide necessary information for the development of clinical treatment practices and guidelines.

I.4 Research hypotheses and objectives

We hypothesized that hyperthyroidism is associated with an increased risk of breast cancer and hypothyroidism with a decreased risk of breast cancer. We hypothesize that these associations are due to (1) changes in blood levels of thyroid hormones, which can be affected by treatments, comorbidities, and reproductive factors; and (2) partly RAI exposure, which is one of the principal treatment modalities of hyperthyroidism.

Therefore, the principal objective of this thesis project was to study the association between thyroid dysfunction and breast cancer risk among adult women, while investigating possible confounding and modifying effects of thyroid dysfunction treatments, comorbidities, and other breast cancer risk factors.

This thesis aims to address the following specific objectives:

- To estimate the association between thyroid dysfunction and breast cancer risk among women in the UK Biobank population, while accounting for the effect of treatments, and reproductive factors
- To summarize the available evidence in the literature on the association between thyroid dysfunction and breast cancer risk in a systematic review and meta-analysis
- To evaluate the dose-response relationship between radioactive iodine and breast cancer risk among women treated for thyroid cancer and included in a European pooled cohort

Chapter II Materials

In this chapter, we present an overview of the two cohorts that we used in the thesis project: the UK Biobank cohort, and a European pooled cohort of thyroid cancer survivors. The chapter describes general information on the population sources, available data, and data sources of each cohort.

II.1 UK Biobank cohort

II.1.1 Overview

The UK Biobank cohort (UKB) is a population-based cohort, which aims to support the investigation on risk factors for major diseases in middle-aged and senior adults and help to improve the prevention, diagnosis, and treatment of diseases. UKB has approval from the North West Multi-center Research Ethics Committee, which covers the UK. The UKB has also been approved by the National Information Governance Board for Health & Social Care (England and Wales), and the Community Health Index Advisory Group (Scotland) to have access to information that would allow inviting people to participate. From 2006 to 2010, the UKB recruited around 500,000 volunteers aged 40-69 residing across the UK (Figure 8) through invitations to a baseline visit assessment with a response rate of 5.5% (84).

Figure 8 Locations of UKB assessment centers throughout the United Kingdom

The UKB encompasses a wide range of detailed information. At the UKB baseline visit assessment, participants gave informed consent and had a self-completed touchscreen questionnaire, an interview with trained nurses on personal and family medical history, lifestyles, socioeconomic characteristics, as well as physical and cognitive measurements, and blood, urine, and saliva samples collected (Table 5). The UKB is also linked to routine data available from the national hospital inpatient diagnostics and procedures, cancer, and death registration, which provides information on past health-related characteristics and helps to ensure comprehensive follow-up information (Table 6). Additionally, up to 2021, the UKB has conducted three repeat assessment visits on subsets of the cohort in 2012-2013 (n=20,334), 2014 (n=48,999), and 2019 (n=3,478).

In general, the UKB participants were more likely to be older, to be female, to live in less socioeconomically deprived areas than nonparticipants, and to have lower rates of all-cause mortality and cancer incidence than the general population (85). However, thanks to the large numbers of participants with different levels of the relevant risk factors, the cohort is capable of yielding a valid generalizable measure of associations between risk factors and subsequent health outcomes (86).

Table 5 Data collected at the baseline assessment

Questionnaire and interview	
Sociodemographic	Social class; ethnicity; employment status; marital status; education; income; car ownership
Family history and early life exposures	Family history of major diseases; birth weight; breastfeeding; maternal smoking; childhood body size; residence at birth
Psychosocial factors	Neurosis; depression (including bi-polar spectrum disorder); social support
Environmental factors	Current address; current (or last) occupation; domestic heating and cooking fuel; housing; means of travel; shift work; mobile phone use; sun exposure
Lifestyle	Smoking; alcohol consumption; physical activity; diet; sleep
Health status	Previous medical history; regular medications at baseline; disability; hearing; sight; sexual and reproductive history
Hearing threshold	Speech reception threshold[1]
Cognitive function	Pairs matching; reaction time; prospective memory[1]; fluid intelligence[1]; numeric memory[2]
Physical measures	
Blood pressure and heart rate	Two automated measures, one minute apart
Grip strength	Left- and right-hand grip strength
Anthropometrics	Standing and sitting height; weight and bio-impedance; hip and waist circumference
Spirometry	Up to three measures
Bone density[3]	Calcaneal ultrasound
Arterial stiffness[4]	Pulse wave velocity
Eye examination[5]	Refractive index, intraocular pressure; acuity; retinal photograph; optical coherence tomography
Fitness test[5]	Cycle ergometry with electrocardiogram (ECG) heart rate monitoring

Table 5 Data collected at the baseline assessment (continued)

Biological samples	
Blood sample	Blood counts, blood biochemistry, infectious disease antigen, NMR metabolomics
Saliva sample	
Urine sample	

[1] assessed in 170,000 participants;
[2] assessed in 50,000 participants;
[3] measured in one heel for 170,000 participants and both heels for 320,000 participants;
[4] measured in 170,000 participants;
[5] measured in 100,000 participants
Reprinted from Sudlow C et al, 2015 (87)

Table 6 Details on UKB linked registrations

Registration	Data Provider	International Classification of Diseases (ICD)		Classification of Interventions and Procedures (OPCS)		Period of data currently available
		ICD9	ICD10	OPCS3	OPCS4	
Hospital Admissions (Inpatients)						
Hospital Episode Statistics for England	NHS Digital		1997 onwards		1997 onwards	1997 onwards, with critical care data from 2011
Scottish Morbidity Record	Information and Statistics Division, Scotland	1981 - 1996	1996 onwards	1977 - 1988	1989 onwards	1981 onwards
Patient Episode Database for Wales	Secure Anonymised Information Linkage, Wales		1999 onwards		1999 onwards	1998 onwards
Cancer						
England & Wales	NHS Digital	1979 - 1994	1995 onwards			1971 onwards
Scotland	National Records of Scotland, NHS Central Register	1980 - 1996	1997 onwards			1957 onwards
Death						
England & Wales	NHS Digital		2006 onwards			2006 onwards
Scotland	NHS Central Register, National Records of Scotland		2006 onwards			2006 onwards

NHS: National Health Service. The Scottish hospital inpatient data does not currently include psychiatric or maternity admissions. Reprinted from https://biobank.ndph.ox.ac.uk/showcase/exinfo.cgi?src=Data_providers_and_dates

II.1.2 Baseline assessment

II.1.2.1 General process at baseline assessment: Questionnaire and interview

At the baseline assessment, a touch-screen self-administered questionnaire was used to collect a wide range of information (Table 5), which took participants about 30 minutes to complete

with the help of a staff member if required. Information that is not readily collected via the touch-screen system (e.g. not involving categorical or numerical responses; requires detailed questioning) is collected in a subsequent 5-10 minute computer-assisted personal interview (88).

Because the procedure to identify personal medical history is the main focus of our project and it required using information from different sources simultaneously, in the following text, we will present in detail the data collection procedure on personal medical history only. Details on other areas covered in the touch-screen questionnaire and the interview that were used in our project can be found in the Appendix 1 and the UKB website (https://biobank.ndph.ox.ac.uk/showcase/browse.cgi).

II.1.2.2 Personal medical history assessment

Questions regarding the participants' medical history in the questionnaire and during the interview are listed in Table 7. If a participant indicated on the touch-screen that they had particular medical conditions, underwent operations or were taking prescribed medications, they would be asked to specify the information, and the interviewer would subsequently record the information, using pre-coded lists built into the computer-assisted personal interview system, along with structured search facilities.

The tree structure for medical conditions and operation were based on/derived from the 10th revision of International Classification of Diseases coding (ICD-10) (88). The interviewer would also ask the participants to indicate the year/age at the first diagnosis for each medical condition reported or when the procedure had taken place for each operation reported. Information on cancer histopathological diagnoses or specific anatomical locations was not recorded during the interview. If medical conditions or operations could not be found in the operations tree, it was typed free-text entry, which was subsequently coded by medical-trained UKB staff.

Only information about regular taking medications, i.e. any regular treatments taken weekly, monthly, or 3 monthly (e.g., depot injections), would be recorded. Short-term medications or medications that had been stopped taking would not be included. The UKB treatment list does not systematically provide doses and formulations.

Table 7 Questions to collect information on medical history during the baseline assessment visit

Information scope	Touch-screen questionnaire	Interview
Cancer	Has a doctor ever told you that you have had cancer?	In the touch-screen you selected that you have been told by a doctor that you have cancer, could you now tell me what type of cancer?
Non-cancer conditions[1]	Has a doctor ever told you that you have had any other serious medical conditions or disabilities?	In the touch screen you selected that you have been told by a doctor that you have other serious illnesses or disabilities, could you now tell me what they are?
Medications[2]	Do you regularly take any other prescription medications? (Do not forget medications such as puffers or patches)	In the touch screen you said you are taking regular prescription medications. Can you now tell me what these are?
Operations[3]	Have you had any major operations?	In the touch screen you said that you have had a major operation. Could you now tell me what the operation was?

[1] Non-cancer conditions other than heart attack, angina, stroke, high blood pressure, blood clot in leg (DVT), blood clot in lung, emphysema/chronic bronchitis, asthma or diabetes, which were addressed in another question in the questionnaire

[2] Medications that do not belong to any of the following classes of medications: blood pressure lowering, cholesterol lowering, hormone-replacement therapy or oral contraceptive pills, which were addressed in another question in the questionnaire

[3] Operations other than hysterectomy and bilateral oophorectomy, addressed in another question in the questionnaire

II.1.3 External linkage

The UKB is linked to the national hospital inpatient diagnostics and procedures, cancer, and death registration, using multiple identifiers, including NHS number NHS number in England and Wales and the Community Health number in Scotland (which is the most reliable identifier), name, date of birth, address, general practice, mobile telephone numbers and e-mail addresses (88). External data providers and the period of data currently available are presented in the Table 6. The available information in the UKB is presented in the Table 8.

II.1.3.1 Cancer registries

Completeness – the extent to which all of the incident cancers occurring in the population are included in the registry database – is a very important aspect of data quality. According to a Cancer Incidence in Five continents publication, two indices could be used to evaluate the completeness of a cancer registry: the proportion of cases microscopically verified, and death certificate methods (89). In the National Cancer Registration in England, 85.3% of all malignant tumors were microscopically verified in 2016. The registrations based solely on death

certificate information represented more than 8% of cancers in the 1980s and have been reduced to less than 1% of all registrations in 2016 (90). The English national cancer registry has also been assessed against randomized controlled trials data, inpatient hospital data, and simulation, with positive results (91-93). The validity, comparability, and timeliness of the national cancer registration data are tested and published alongside the national statistics of both cancer incidence and survival (90). For more than 10 years the number of serious errors in the cancer registries has consistently been 0.1% or less (94).

Table 8 Available information in the UKB external sources

Sources	Available information
Cancer registries	Date of cancer diagnosis
	Age at cancer diagnosis
	Type of cancer: ICD-10, ICD-9,
	Reported occurrences of cancer
	Histology code
	Behavior code
Death registries	Date of death
	Primary causes of death: ICD-10
	Contributory causes of death: ICD-10
Hospital inpatient databases	Diagnosis codes: ICD-9 or ICD-10
	Diagnosis dates
	Operations and procedural codes: OPCS-3 or OPCS-4
	Operations and procedural dates
	Data related to maternity-related admissions
	Data related to psychiatric admissions
	Administrative details (e.g. admission and discharge date) and the organization providing the treatment

ICD: International Classification of Diseases, OPCS: Classification of Interventions and Procedures

II.1.3.2 Death registries

National death registrations in the UK are virtually complete. Only a very small percentage of deaths remain legally uncertified (0.4%) (i.e without being certified by doctor or referral to coroner) and the presumption of death act is <0.1%. Only 0.1% of deaths have their underlying cause amended (95, 96).

The data UKB received from the death registry includes the date of death and the primary and contributory causes of death, coded using the ICD-10 system.

II.1.3.3 Hospital inpatient databases

Inpatients are patients who are admitted to the hospital and occupy a bed. This includes admissions where an overnight stay is planned and day cases. It is estimated that 98–99% of hospital activity in England is funded by the publicly funded healthcare system (National Health Service - NHS), and be recorded in hospital inpatient databases (97). The validity of key fields in inpatient databases is generally high, ranging from 100% for treatment function to 92.3% for sites of treatment. Data is estimated to be 93% accurate (98).

All datasets currently available contain data on admissions and discharge, diagnostic and operation codes, except for maternity and psychiatric admissions for Scotland.

II.2 Concerted action FI4P-CT98-0078: A European pooled cohort of thyroid cancer survivors

II.2.1 Overview

The concerted action FI4P-CT98-0078 is a European project, of which the objective is to establish a common database pooling the European cohorts of patients who received high activities of radioactive iodine for the treatment of a thyroid cancer in order to improve the epidemiological knowledge on the risk of cancers and leukemia occurring following exposure to high activities of radioactive iodine during adulthood.

The concerted action was first set up in 1999. At that time, the risk of cancer and leukemia after administration of high activities of radioactive iodine has been studied in three major European cohorts in French, Sweden, and Italy. The three cohorts were population-based and included patients with a histologically confirmed papillary or follicular thyroid cancer diagnosis as the first primary cancer. In brief, the Swedish cohort included patients treated for thyroid cancer between 1950 and 1983 in six university hospitals. The Italian cohort consists of patients treated for thyroid cancer between 1958 and 1996 at the nuclear medicine department of the General Hospital in Busto Arsizio, Italy. The French cohort included patients treated for thyroid cancer between 1934 and 2005 in four hospitals (Villejuif, Reims, Caen, and Saint Clouds). The concerted action has allowed to standardize the dosimetry of radioactive iodine and external beam radiotherapy of the three cohort studies.

Within the framework of the concerted action, the three original cohort studies (99-102), has been updated between 1997 and 2015 to include 2,202 and 92 new patients from the French and Italian cohorts, respectively, who were initially treated during the period 1995-2005. We extended the follow-up time up to 7, 11, and 20 years for the Swedish, Italian, and French cohorts, respectively (Figure 9).

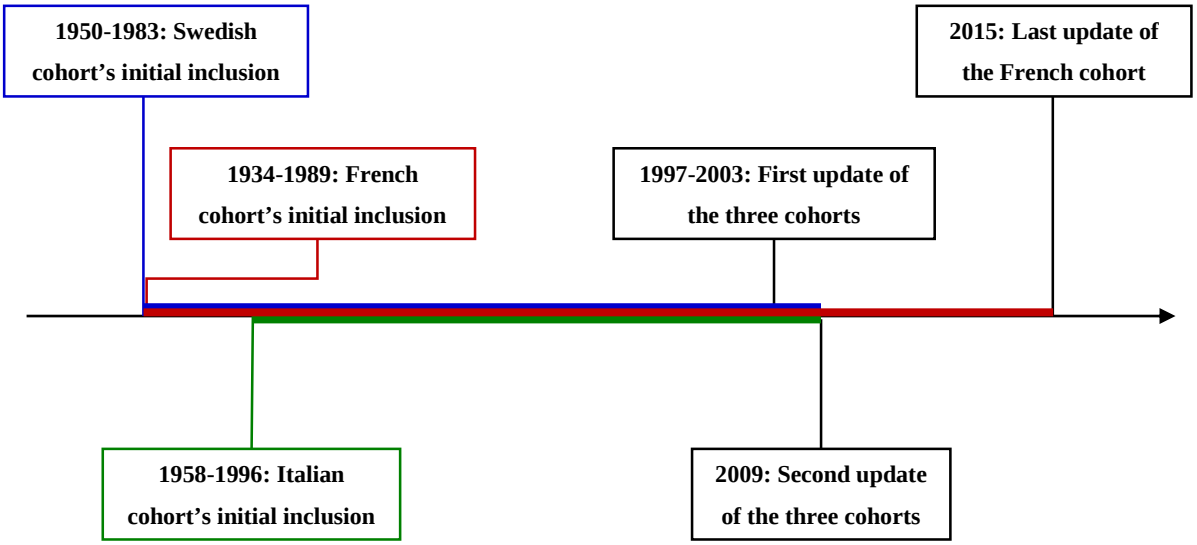


Figure 9 Timeline of the original studies and three updates within the frame of the concerted action FI4P-CT98-0078

In total, the pooled cohort is comprised of 12,916 patients, of whom 9,372 were women and 7906 had received therapeutic activities of radioactive iodine (99-102). We have access to medical records of thyroid cancer patients in all cancer centers, which generate detailed information on thyroid cancer diagnosis, and treatment modalities for thyroid cancer. Moreover, the pooled cohort encompasses information from medical records of patients' follow-up visits in the French and Italian cohorts. The Swedish cohort is linked to the cancer and death national registration, using individuals' unique identifier.

The French cohort's protocol has been approved by the French National Agency regulating Data Protection (CNIL), and consent was obtained from the study participants. The Swedish cohort obtained approval of the Swedish data inspection board. Because the sole aim of the Italian cohort is to evaluate the safety of radio-iodine treatment administrated by medical doctors of this hospital, without any other specific contact of patients, no special authorization has been needed for this population. The pooled cohort study contains only pseudonymized individual data.

II.2.2 Reconstruction of the incidental dose to the breast

Because ionizing radiation effects depend on the doses absorbed by the target organ, we reconstructed doses incidentally delivered by the two sources of high exposure in the thesis project, RAI administration, and external radiotherapy.

We estimated the mean RAI absorbed dose, D_{r_T} (Gy), incidentally delivered to the target organ r_T (i.e., the breasts), by N administrations of RAI either for diagnostic or therapeutic purposes, for women aged >15 years at thyroid cancer diagnosis, using the Medical Internal Radiation Dose's formula (103):

$$D_{r_T} = \sum_{n=1}^{N} \left(A_{0,n} \times \sum_{r_S=1}^{N_S} \tilde{a}(r_S, T_D) \times S(r_T \leftarrow r_S) \right)$$

where N, the number of administrations of RAI; $A_{0,n}$, the administered activity for the nth treatment (Bq); N_S, the number of source organs; T_D, the dose-integration period (s); $\tilde{a}(r_S, T_D)$, the time-integrated activity coefficient for the source organ r_S (s); $S(r_T \leftarrow r_S)$, the value representing the mean absorbed dose rate per unit activity from source organ to target organ (Gy/(Bq.s)). The S values vary according to the source-target region pair (104, 105), and were computed with the reference female voxel phantoms developed by the International Commission on Radiological Protection (106). The time-integrated activity coefficients $\tilde{a}(r_S, T_D)$ were estimated using data of patients treated for a thyroid cancer in a previous study (107) (Appendix 6). RAI activities for diagnostic purposes were not systematically recorded in all cancer centers and when available, the information on whether RAI administration was for diagnostic or therapeutic purposes was not recorded. Therefore, we considered activities of 10 mCi (equivalent to 0.37 GBq) or more as therapeutic RAI and lower activities as RAI for diagnosis. We used data on therapeutic RAI to conduct our main analyses and data on therapeutic and diagnostic RAI for a sensitivity analysis.

External radiotherapy data were obtained from technical radiotherapy records for 503 patients (51.9% of thyroid cancer survivors who received external radiotherapy). For each of these patients, absorbed doses to anatomical organs in the beam and at a distance were estimated using female mathematical phantoms corresponding to the patients' age and height at the time of treatment (108, 109), and radiotherapy equipment parameters at each cancer center. The

phantoms were simulated by a homemade computer program called “Dos_EG”, and provided 188 points of the body for dose distribution estimations (110). For patients with available technical records, we calculated the mean dose to five points located at four different quadrants (upper-inner, lower-inner, upper-outer, lower-outer) and the nipple of each breast, and subsequently calculated the mean dose to the left and the right breasts. We performed nearest neighbor hot-deck imputation (111, 112) within each cancer center for 467 (48.1%) patients without the necessary data.

Chapter III Overview of statistical methodology

This chapter describes different statistical methods used during the thesis, explaining the basic notions, and the rationale of the methodological approaches. The methods are presented in the order that the part of interest arises in the next chapters of the thesis: Cox proportional hazards models and meta-analysis (Chapter IV), Poisson regression models (Chapter V), and mediation analyses (Chapter VI).

III.1 Cox proportional hazards models

III.1.1 Definition

First introduced in 1972 by Sir David Cox (113), the Cox proportional hazards model is a regression model commonly used in medical research for investigating the association between the survival/time-to-event and one or more independent variables. In a Cox proportional hazards model, the measure of effect is the hazard function, which is the risk of having the event of interest, given that the participant with a set of p covariates X = (X_1, X_2,… X_p) has survived up to a specific time t, which can be written as following:

$$h(t) = h_0(t) * \exp(\beta_1 X_1 + \beta_2 X_2 + \cdots + \beta_p X_p) \quad (1)$$

in which, $h(t)$ denotes the hazard function, $h_0(t)$ presents the baseline hazard when all independent variables are equal to 0, and β_1, β_2, …β_p are the corresponding coefficients of X_1, X_2,… X_p. In the equation (1), the time to event is only expressed in $h_0(t)$, which is non-parametric and cannot be estimated from the model. In contrast, the Cox proportional hazards model allows us to estimate the individual risk associated with an independent variable by calculating a hazard ratio (HR) , i.e exponential of the corresponding coefficient β. For example, the hazard ratio associated with a binary variable X_i is calculated as following:

$$HR(t) = \frac{h(t, X_{i1})}{h(t, X_{i2})} = \frac{h_0(t) * \exp(\beta_i X_{i1})}{h_0(t) * \exp(\beta_i X_{i2})} = \exp(\beta_i (X_{i1} - X_{i2}))$$

Thus, by taking the natural logarithm, the Cox proportional hazards model can be expressed as multiple linear regression. Estimation of parameters in the Cox model can be obtained using maximum likelihood estimation and the corresponding profile likelihood ratio confidence

intervals could also be estimated. An HR that is significantly superior to 1 indicates a positive association between the variable of interest and the time-to-event outcome while an HR inferior to 1 demonstrated an inverse association.

In this thesis project, we used the Cox proportional hazard model to estimate the association between thyroid dysfunction and breast cancer risk in UK Biobank (UKB) female participants (Chapter II.1 and Chapter IV).

III.1.2 Time-dependent variables

In the equation (1), all independent variables do not vary according to the time in the study. However, in many instances, data on independent variables are collected longitudinally and those variables may change over time. For example, a woman with no thyroid dysfunction at baseline may be diagnosed with hyperthyroidism at the time t during the follow-up and therefore, she may contribute person-time to both categories: no thyroid dysfunction before t and hyperthyroidism after t. The Cox proportional hazards model thus could be modified as following:

$$h(t) = h_0(t) * \exp(\beta_1 X_1 + \beta_2 X_2 + \cdots + \beta_i X_i + \beta_{i+1} X_{i+1}(t) + \ldots + \beta_p X_p(t))$$

in which, there are i and $p - i$ time-fixed and time-dependent covariates, respectively. In this thesis project, for the UKB cohort, after the baseline, the status of thyroid dysfunction diagnosis and treatments was updated every 30 days, using the hospital inpatient databases.

III.1.3 Model assumptions

Proportional hazards: One of the most important assumptions of the Cox model is that the hazard ratio for a given covariate, i.e the association between the covariate and the time-to-event outcome, is constant over time. In this project, we graphically evaluated the assumption based on plots of scaled Schoenfeld residuals against time and tested the assumption by introducing an interaction term between covariates and follow-up time. We found no evidence of assumption violation.

Log-linearity: The Cox model assumes that continuous covariates have a log-linear form, i.e the change of hazard ratio for each increasing unit of the covariate is constant and equal to the corresponding coefficient regardless of the covariate value of the covariate. To test the

assumption, one can (1) incorporate both continuous covariates and the corresponding categorical covariates (e.g. the quartiles of continuous variables), and test the null hypothesis that all the coefficients associated with the categorical covariates are zero, or (2) plot the martingale residuals against the fitted value of continuous covariates. If the assumption is not satisfied, the non-linear continuous covariates should be transformed before introducing them into the models. In the project, we used both aforementioned methods and found no violation of log-linearity assumption for age at baseline, BMI, age at menopause, age at menarche. However, in our study, most covariates were used as categorical variables.

III.1.4 Confounding effects and effect modification

Confounding effects: Maldonado and Greenland have discussed several strategies to assess confounding effects of a given covariate (114): (1) the "change-in-estimate" strategy, in which a variable is controlled if the adjusted and unadjusted estimates differ by some important amount; (2) the "significance-test-of-the-covariate" strategy, in which a variable is controlled if its coefficient is significantly different from zero at some predetermined significance level; (3) the "significance-test-of-the-difference" strategy, which tests the difference between the adjusted and unadjusted exposure coefficients; (4) the "equivalence-test-of-the-difference" strategy, which significance-tests the equivalence of the adjusted and unadjusted exposure coefficients; and 5) a hybrid strategy that takes a weighted average of adjusted and unadjusted estimates. Following the authors' recommendation on the performance of these strategies, we chose to consider confounding factors that make the regression coefficient changing by more than 10%.

Effect modification: Effect modification was evaluated by testing the statistical significance of an interaction term between thyroid dysfunction and the studied covariate [likelihood-ratio χ^2 tests for heterogeneity (categorical variables) and linear trend (continuous variables)]. Because the multiplicative interactions do not fully reflect the size of the interaction and the public health importance, when interaction was statistically significant at the multiplicative scale, we reported results for both additive and multiplicative interactions (23).

III.1.5 Competing risks

A competing risk is an event that precludes the occurrence of the primary event of interest. Two common approaches to assess competing risks were cause-specific hazards models and

subdistribution hazards models. Cause-specific hazards models refer to the hazard rate of the event of interest in the presence of competing risks in individuals who have survived up to time t without either the event of interest or the competing risks. Subdistribution hazards models, on the other hand, regard the hazard rate in individuals who have not experienced the event of interest with or without failing from competing events. It is recommended that cause-specific hazards models are better suited for studying the etiology of diseases while subdistribution hazards models should be used in predicting an individual's risk (115). In the present project, we considered death and diagnosis of cancer other than breast cancer as competing risks and we used cause-specific hazards models to assess competing risk effects.

III.2 Meta-analysis

Meta-analysis is a method of evidence synthesis which aims to combine, summarize and interpret all available evidence regarding an explicit research question in a quantitative way, following a predefined, systematic, and reproducible protocol. In this thesis project, we conducted a meta-analysis to synthesize evidence across previous studies on the association between thyroid dysfunction and breast cancer risk, to estimate the magnitudes and variation and to analyze the factors that influence the association (Chapter IV).

III.2.1 Pooled risk estimates

In a meta-analysis, because the precision level of risk estimates can vary across studies, each included study would be assigned a weight according to the level of information that they carry before being aggregated to obtain the combined effect. To decide the weight of each study and combine their risk estimates, the fixed effect model and the random effects model are traditionally used (116).

The fixed-effect model assumes that all effect sizes come from a single, homogeneous population and all studies share a common constant effect size. In other words, this model supposes no sampling error between studies. For binary effect size data, the most common approach to calculate method to calculate the weighted average is Mantel-Haenszel’s method (116, 117). However, in reality, it is implausible to impose that all the populations in epidemiological studies included in a meta-analysis are identically homogeneous.

The random-effects model assumes that there is not only one true effect size but a distribution

of true effect sizes (116). The combined effect therefore cannot represent the one common effect, but instead represents the mean of the population of true effects. This type of model allows errors both within study and between studies. In the random effects model for a meta-analysis, the formula to calculate an adjusted random-effects weight w_i for each observation is the following

$$w_i = \frac{1}{s_i^2 + \tau^2}$$

In which s_k^2 and τ^2 are the within study- and between studies-variance, respectively. τ^2 can be computed using the DerSimonian-Laird estimator. The combined effect θ can be calculated using the obtained random-effects weights, the effect size of included studies θ_i, and the inverse variance method

$$\theta = \frac{\sum_{i=1}^{n}(\theta_i w_i)}{\sum_{i=1}^{n} w_i}$$

III.2.2 Heterogeneity test

It is important to consider to what extent the results of studies are consistent. For this purpose, Cochran's Q test (Cochran 1954), which is calculated as the weighted sum of squared differences between individual study effects and the pooled effect across studies, can be used. A low p-value of the test provides evidence of heterogeneity of intervention effects (variation in effect estimates beyond chance) (116).

$$Q = \sum_{i=1}^{n} w_i(\theta_i - \theta)^2$$

Along with testing whether heterogeneity is present with Cochran's Q test, methods have been developed for quantifying inconsistency across studies to assess its impact on the meta-analysis, one of which is the I_2 statistics (116):

$$I^2 = \frac{Q - df}{Q} * 100\%$$

This describes the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error. The importance of inconsistency depends on several factors. In

general, the following thresholds for the interpretation of I^2 could be considered: 0% to 40% as might not be important; 30% to 60% as may represent moderate heterogeneity; 50% to 90% as may represent substantial heterogeneity; 75% to 100% as considerable heterogeneity (116).

Moreover, to assess if the combined effect estimate is robust, and does not depend heavily on one single study, influence analysis can be conducted with the leave-one-out method (118). In this approach, the results of the meta-analysis would be recalculated n times, each time leaving out one study, and be sorted by effect size and I_2 value. If the direction and the magnitude of the results do not change considerably, there is no influential study in the meta-analysis.

III.2.3 Publication bias

Publication bias occurs when results of published studies are systematically different from results of unpublished studies, which subsequently causes a biased combined effect in a meta-analysis (119). Publication bias arises as in general, studies with statistically significant or positive results are more likely to be published than those with nonsignificant or negative results. Based on the idea that selective reporting causes a study's effect size to depend on its sample size, one of the methods to address publication bias is funnel plot, which is a scatter plot of the studies' observed effect sizes on the x-axis against a measure of their standard error on the y-axis (119). In the absence of publication bias, the data points in such a plot should form a roughly symmetrical, upside-down funnel. To assess the presence of funnel plot asymmetry quantitatively, Egger's test is commonly used (119). The test is based on a simple linear regression model:

$$\frac{\theta_i}{SE_{\theta_i}} = \beta_0 + \beta_1 \frac{1}{SE_{\theta_i}}$$

In which, SE_{θ_i} is the standard error of the observed effect size θ_i. To evaluate the funnel asymmetry, we inspect the size of β_0, and if it differs significantly from zero. When this is the case, Egger's test indicates funnel plot asymmetry.

III.3 Dose-response models: An application of the Poisson regression models

III.3.1 Definition

Poisson regression models are a type of generalized linear model that is commonly used in epidemiology for modeling count data (120). Assuming the rate ratio associated with an exposure of interest X is constant across a series of time intervals, Poisson regression models can be used to model the observed number of events by time interval and dose exposure. Data is organized in a multi-way contingency table of k dose categories of X and j strata, which present the rate of event occurrence λ_j according to the time interval and covariates other than X. The observed number of event n_{jk}, the total person-year PY_{jk}, the rate of event occurrence λ_{jk}, and the mean dose of exposure d_{jk} are assigned in each cell of the contingency table. Regarding n_{jk} follows a Poisson distribution with the parameter λ_{jk}, the expected number of event N_{jk} in each cell can be estimated as $N_{jk}=PA_{jk}* \lambda_{jk}$. Thus, the relative risk associated with the exposure of interest RR_{jk} is equal to λ_{jk}/ λ_j. In case that one compares the number of observed events with the expected number of events in a standard population, the rate ratio λ_{jk}/ λ_j is considered as standardized incidence/mortality ratio. To investigate the risk associated with a dose-effect of exposure, the RR_{jk} often takes the form $RR_{jk} = \exp(\beta * d_{jk})$. In summary, the relative risk associated with X in the population is modeled as $RR = w_{jk} * \lambda_j * \exp(\beta * d_{jk})$ where w_{jk} denotes the weighting according to PA_{jk}. Meanwhile, the absolute excess risk (AER) could be calculated as the observed minus expected number of neoplasms, divided by the person-years at risk and multiplied by a constant of person-year of interest (10,000 or 100,000 person-years).

Estimation of parameters in the Poisson model can be done using maximum likelihood estimation. The corresponding profile likelihood ratio and Wald confidence intervals could be estimated. The latter assumes that the maximum likelihood estimation follows a normal distribution, which is a strong assumption. Therefore, the profile likelihood ratio is often preferred.

However, relative risk is often not used as a common effect measurement in radiation epidemiology, but the excess relative risk (ERR) and absolute excess risk (AER) . Using ERR

supposes that the risk increased proportionally with each increasing unit of radiation while using AER requires the assumption that radiation induces an additional risk above the baseline risk of the population. ERR and AER can be expressed as following

$$ERR = w_{jk} * \lambda_j * \left[1 + \exp\left(\beta * \rho(d_{jk})\right)\right]$$

$$AER = w_{jk} * \lambda_j + \exp\left(\beta * \rho(d_{jk})\right)$$

in which, $w_{jk} * \lambda_j$ is often considered as population background rate, which can be parameterized, $\rho(d_{jk})$ denotes the shape of the dose-response models depending on the radiation dose, and λ_j is often considered the baseline rate of the population without exposure.

In this thesis project, we used the Poisson regression models to investigate the dose-response relationship between RAI and breast cancer risk among female thyroid cancer survivors in the European pooled cohort (Chapter II.2 and Chapter V).

III.3.2 Time-dependent variables

Within the contingency table, the inclusion of a time-dependent variable could be accounted for by adding an extra dimension. The level of the time-dependent variable is updated for each unit of time interval while time-fixed covariates are assigned and the event of interest and the person-year are counted as normal. If the unit of the time interval is wider than the unit of time update for the time-dependent variables (for example, a year vs a date), the status of the time-dependent variable could be evaluated at the mid-point of the time interval.

III.3.3 Effect modification

To account for a modifying effect, one could introduce into the models for ERR or AER a new term representing the effect modifier as following

$$ERR = w_{jk} * \lambda_j * \left[1 + \exp\left(\beta * \rho(d_{jk}) * f(z)\right)\right]$$

$$AER = w_{jk} * \lambda_j + \exp\left(\beta * \rho(d_{jk}) * f(z)\right)$$

in which, z denotes the effect modifier and $f(z)$ describes the effect of z on the radiation effect, often in the form as $(1 + \exp(z))$. Possible effect modifications by external radiotherapy,

age/year at diagnosis, and follow-up time were evaluated.

III.4 Causal framework - Mediation analyses

III.4.1 Traditional approaches vs counterfactual framework approach

Mediation analysis is statistical methods which are used to evaluate the causal sequence where an independent variable causes one or several mediating factors that, in turn, cause an outcome of interest (Figure 10). Regarding a possible causal relationship, one could expect to investigate the causal effect through the effect of the independent variable on the outcome directly (directed effect) and the effect that goes through mediators (indirect effect) (121).

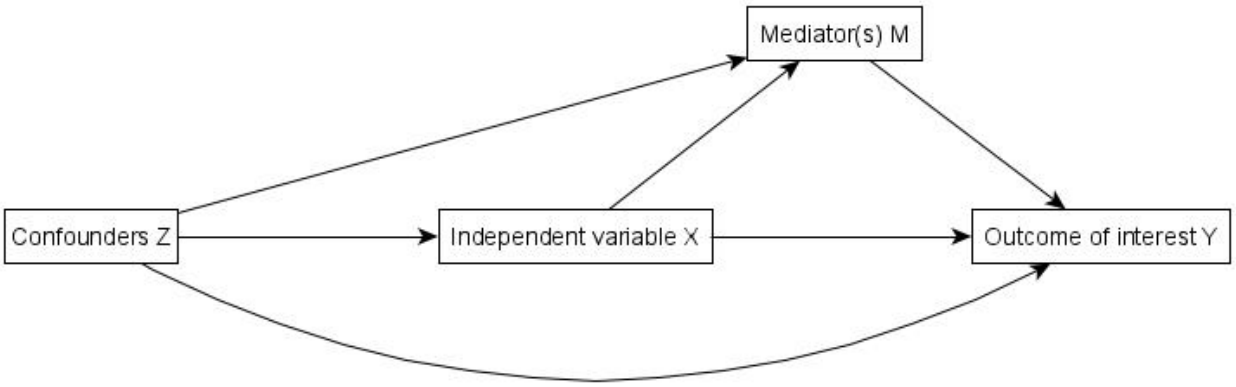


Figure 10 A simple directed acyclic graph

Two traditional approaches, the difference method and the product method, are based on the comparison between two regression models, one with and one without conditioning on the mediator (**Appendix 2**). The traditional methods, although widely used, had unavoidable limitations: (1) they assume no mediator-exposure interaction, a linear mediator-outcome relationship, and in case of a binary outcome, a rare outcome, (2) they cannot handle multiple mediators, (3) they are prone to be biased when accounting for confounding factors between mediator – outcome (collider bias) (121, 122). Recent progress in methods for mediation analysis that involves applying the causal inference approach is capable to overcome the aforementioned shortcomings. Assuming multiple parallel and sequential mediators exist in the association between thyroid dysfunction and breast cancer risk, and they are not independent, we recommend the mediation causal inference approach in future research. Details on how mediation causal inference could be applied is presented in Chapter VI.4.3.

III.4.2 Mediation causal inference

The three principal steps in the causal inference analysis are effect definition, identification, and estimation (123).

III.4.2.1 Effect definition

Effect definition aims to frame the research question and to determine which type of effect suits best. There are approaches to account for different types of effect: natural (in)direct effects, interventional (in)direct effects, controlled direct effects…, which, in turn, address different types of research questions, require different assumptions, and involves various ways of effect decomposition (Appendix 3) (123).

Natural and interventional effects measure the exposure effect that would be realized while controlling the mediator distribution to be fixed. However, while natural effects fix the mediator at the counterfactual mediator value, the interventional effects set the mediator for each subject to a random draw from the distribution of the mediator in the conditional population without the exposure. Natural effects are often criticized for their reliance on a hypothetical world that cannot be verified with randomized control trials and its strong untestable assumptions, i.e. in case of multiple mediators or a mediator which varies over time, natural effects cannot be estimated. Meanwhile, interventional effects reflect realistic settings to test the research question and can be identified under weaker conditions (124).

In the thesis project, we assume that hyperthyroidism caused an increased risk of breast cancer and hypothyroidism caused a decreased risk of breast cancer, either directly or through other factors such as treatments (i.e. RAI) (mediators) and the question of interest is how thyroid dysfunction (exposure) affect breast cancer risk (outcome). We used directed acyclic graphs (DAGs) to visualize different components in our causal analysis (Appendix 4).

III.4.2.2 Effect identification

Effect identification involves determining whether the causal effect of interest is valid using the available data that investigators have. Essential assumptions that must be held to validate causal relationships are (125-128):

- Exchangeability: Different groups are assumed to be conditionally exchangeable when they have the same values of all other factors that can indicate the outcome: No uncontrolled confounding factors between the exposure-outcome, between the exposure-mediators, and between mediators – outcome (124).

  In reality, this assumption is often based on researchers' experience and the available data.

- Positivity: There is a probability greater than zero–a positive probability–of being assigned to each of the intervention levels.

- Consistency: The observed outcome for every individual with a given exposure would not have changed had they been assigned to that exposed group and the observed outcome for every individual in the unexposed group would not have changed had they been assigned to the unexposed group. The assumption demands to refine as much as possible the exposure to have a sufficiently well-defined one. In our project, we assume that once an individual was diagnosed with hyper- or hypothyroidism, the hyper- and hypothyroidism status did not change during the follow-up and that the effects of all levels of thyroid dysfunction are identical, i.e thyroid dysfunction-variation irrelevance.

III.4.2.3 Effect estimation: G-formula

First introduced by Robins in 1986 (129) to estimate the causal effect of a time-depending exposure in the presence of time-depending confounders that are affected by the exposure (i.e mediators), G-formula has been increasingly used for mediation analysis. The basic idea is to model the association between exposure-mediator, and exposure-outcome accounting for the mediator and to use the obtained models to simulate the hypothetical world where the exposure/mediator status would be fixed for the whole population. The procedure of modeling and simulation is conducted forward in time. It begins by partitioning the follow-up time into even, distinct time periods and specifying parametric regression models for the distribution of each time-dependent exposure, mediator, confounder, and survival outcome at each time point based on former covariate values, i.e the status of time-dependent exposure, mediator, confounder, and outcome at the time N+1 is calculated based on data of the times 0 through N. Model parameters generated from these regression models are estimated using maximum

likelihood and used to assign values to the mediator to generate two joint exposure-mediator hypothetic interventions (130). This allows us to compare the outcomes of the same population under different statuses of exposure/mediator, which could be interpreted as a causal effect. The principal steps of the G-formula are resumed in the Figure 11 (131). The survival mediational g-formula can be implemented using the mGFORMULA SAS macro (132).

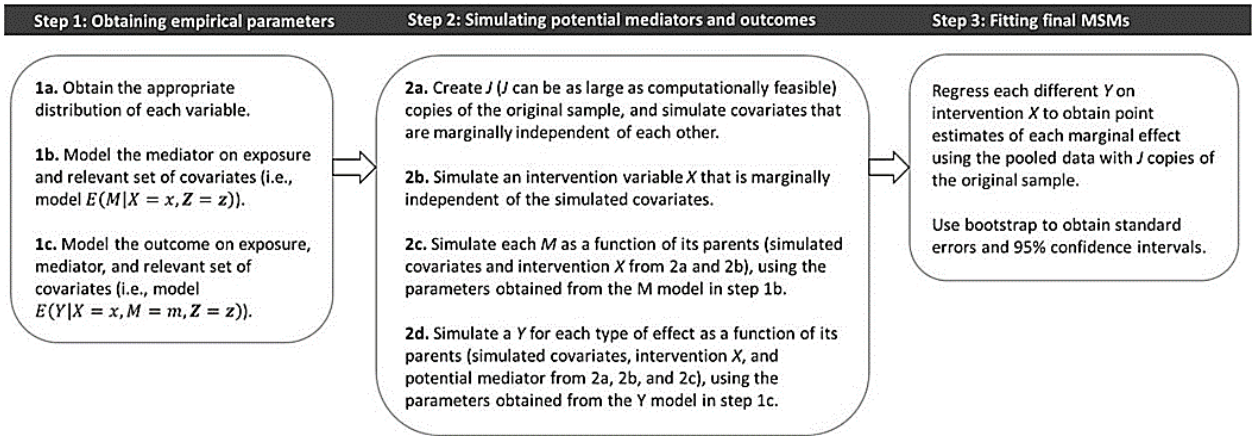


Figure 11 Steps for G-formula marginal structural model in causal mediation analysis. Let Z denote relevant covariates for the association exposure-mediator and exposure-outcome, X denote exposure, M denote mediator, and Y denote the outcome of interest. Variables in step 1 are observed variables whereas variables in step 2 are all simulated variables. Step 1a and 2a combined can be replaced by resampling. Reprinted from Wang A et al. 2015 (131).

Chapter IV Thyroid dysfunction and breast cancer risk

IV.1 Specific objectives

In this chapter, we aimed to estimate the association between hyper- and hypothyroidism and breast cancer risk among pre- and postmenopausal women, and investigate possible confounding or modifying effects of thyroid dysfunction treatments, comorbidities, and breast cancer risk factors. We present results from our cohort study using data from the population-based UK Biobank (UKB) cohort (133), and an updated systematic review and meta-analysis of all available evidence on breast cancer incidence related to thyroid dysfunction. Compared to our original systematic review and meta-analysis that accessed papers through MEDLINE and the COCHRANE library from inception to January 28, 2019 (54), we extended the search up to July 29, 2021, which resulted in 14 studies included in the updated study.

IV.2 Methods

IV.2.1 Cohort analysis

IV.2.1.1 Study population

Among female participants in the UKB cohort (Chapter II.1), we included participants without cancer diagnosis of any type (except non-melanoma skin cancer) that was self-reported or recorded in cancer registries prior to baseline, i.e. the first visit at a UKB center for study enrollment. We excluded women who underwent a mastectomy prior to baseline or had less than one year of follow-up. After exclusions, our study population included 239,436 women (Figure 12). Follow-up time started at baseline and ended at the date of any cancer diagnosis (except non-melanoma skin cancer), mastectomy, death, lost-to-follow-up, or March 31st, 2016, whichever occurred first.

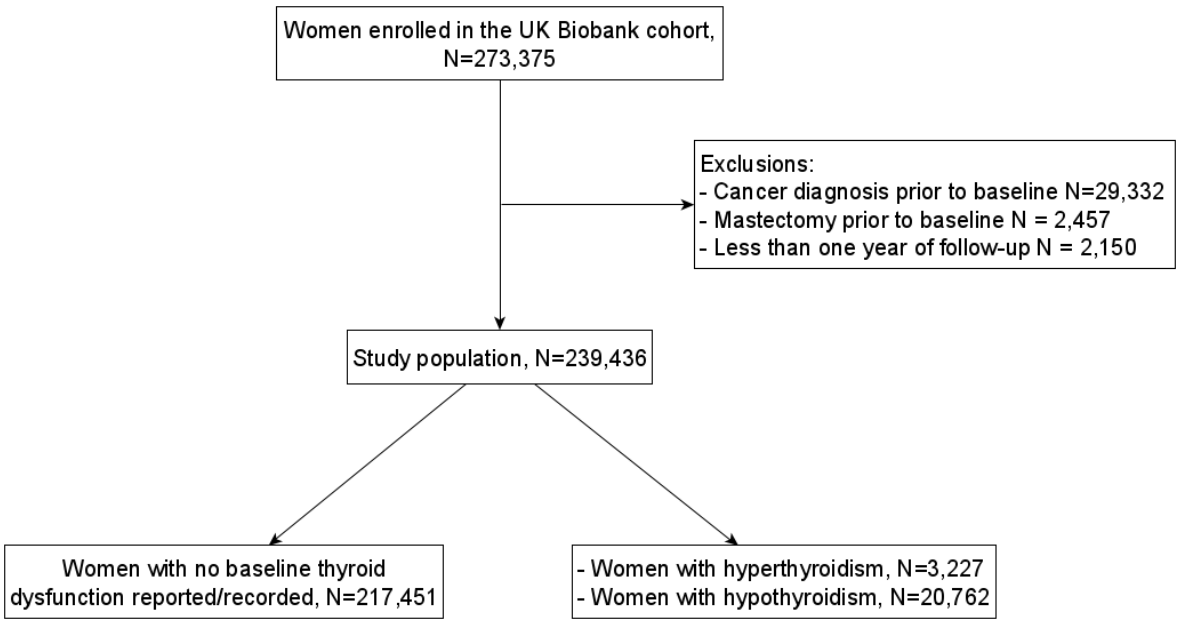


Figure 12 Flowchart of the study which used data from the UK Biobank cohort

IV.2.1.2 Exposure

In the primary analyses, we used information on baseline thyroid dysfunction diagnosis (hyperthyroidism, hypothyroidism, no thyroid dysfunction reported/recorded) and treatments [hyperthyroidism: antithyroid drugs (ATDs) (carbimazole, propylthiouracil), radioactive iodine (RAI), thyroidectomy; hypothyroidism: thyroid hormone replacement therapy (THRT) (liothyronine, thyroxine)] that was self-reported during the baseline interview or recorded (at least once) in a hospital inpatient database prior to baseline (Table 9, Figure 13). Hyperthyroidism and hypothyroidism were assessed separately.

We investigated the following exposure variables: ever diagnosis of hyper-/hypothyroidism, thyroid dysfunction treatment modalities, time since diagnosis, time since treatment onset, age at diagnosis, and calendar year of diagnosis.

IV.2.1.3 Outcome

Breast cancer cases were defined as diagnoses of invasive (n=4,452) or in situ cancers (n=874) recorded in the cancer registries (ICD-10: C50 or D05, ICD-9: 174 or 2330). We considered only the first cancer occurrences. Women diagnosed with cancer of any type during follow-up (except non-melanoma skin cancer) were censored on diagnosis date.

IV.2.1.4 Potential confounders or effect modifiers

We considered comorbidities, and breast cancer risk factors, and healthcare-related factors at baseline as potential confounders or effect modifiers (Appendix 1).

The comorbidities of interest were overweight/obesity, hypertension, diabetes, depression, and autoimmune conditions. Type 1 and 2 diabetes were identified using a modified version of a published algorithm that was developed using the UKB data and validated against external primary and secondary care databases (Appendix 1: Supplementary table 2, Supplementary figure 1) (134). Since thyroid dysfunction etiology was not systematically recorded in the UKB and various autoimmune conditions can occur among patients with thyroid autoimmune diseases such as Graves' or Hashimoto's disease (27), we investigated a potential modifying effect by autoimmune conditions as a proxy for the auto-immune etiology of thyroid dysfunction. We used a variable including any autoimmune condition other than autoimmune thyroid diseases at baseline (Appendix 1: Supplementary table 3) (135-137).

We considered well-established breast cancer risk factors as potential confounders or effect modifiers: menopausal status, age at menarche, parity, age at first birth, family history of breast cancer, use of menopausal hormone therapy (MHT), use of oral contraception, and level of physical activities. Baseline age at menopause was defined as age at bilateral oophorectomy or reported menopause whichever occurred first. If unknown, it was defined in order of priority as age at MHT initiation, or 51 years otherwise. The age threshold corresponds to the median value of age at menopause in the study population.

Other factors suggested to be possibly associated with breast cancer risk in the literature were considered as potential confounders: race, alcohol consumption, and smoking status. Townsend deprivation score of residence, educational attainment, occupation, and adherence to breast and cervical cancer screening programs, which might reflect different levels of health care access and cancer surveillance, were also analyzed as potential confounders.

For all the above-mentioned factors, missing data were infrequent (<5%, except age at menopause: 9.3%), and handled either by defining an "unknown" category (for categorical variables) or imputing the median value in the study population (for continuous variables).

Table 9 Sources of information and coding used to define thyroid dysfunction diagnosis and treatments

		Self-reported data at baseline	Hospital inpatient databases			
			ICD-9	ICD-10	OPCS-3	OPCS-4
Thyroid dysfunction diagnosis						
Hyperthyroidism		Graves' disease Hyperthyroidism Thyroid radioablation therapy Regular use of propilthiouracil or carbimazole at baseline	242	E05	988	X655
Hypothyroidism		Hypothyroidism Regular use of liothyronine or thyroxine at baseline	244, 2452	E02, E032-E039, E063, E089	NA	NA
Thyroid dysfunction treatment						
Hyperthyroidism treatment	Radioactive iodine[1]	Thyroid radioablation therapy	NA	NA	988	X655
	Surgery[1,2]	Thyroidectomy	NA	NA	070, 071, 072	B08
	Antithyroid drugs only[3]	Regular use of propilthiouracil or carbimazole at baseline	NA	NA		
Hypothyroidism treatment	Thyroid hormones	Regular use of liothyronine or thyroxine at baseline	NA	NA		

ICD: International classification of diseases, OPCS: OPCS Classification of Interventions and Procedures, NA: not applicable

1: Only the first definitive hyperthyroidism treatment was considered, e.g. if radioactive iodine occurred before surgery, the treatment modality was coded as "radioactive iodine"

2: Only procedures performed after a diagnosis of hyperthyroidism were considered

3: If patients were treated with both antithyroid drugs and radioactive iodine/surgery, the treatment modality was coded as "radioactive iodine" or "surgery", whichever occurred first

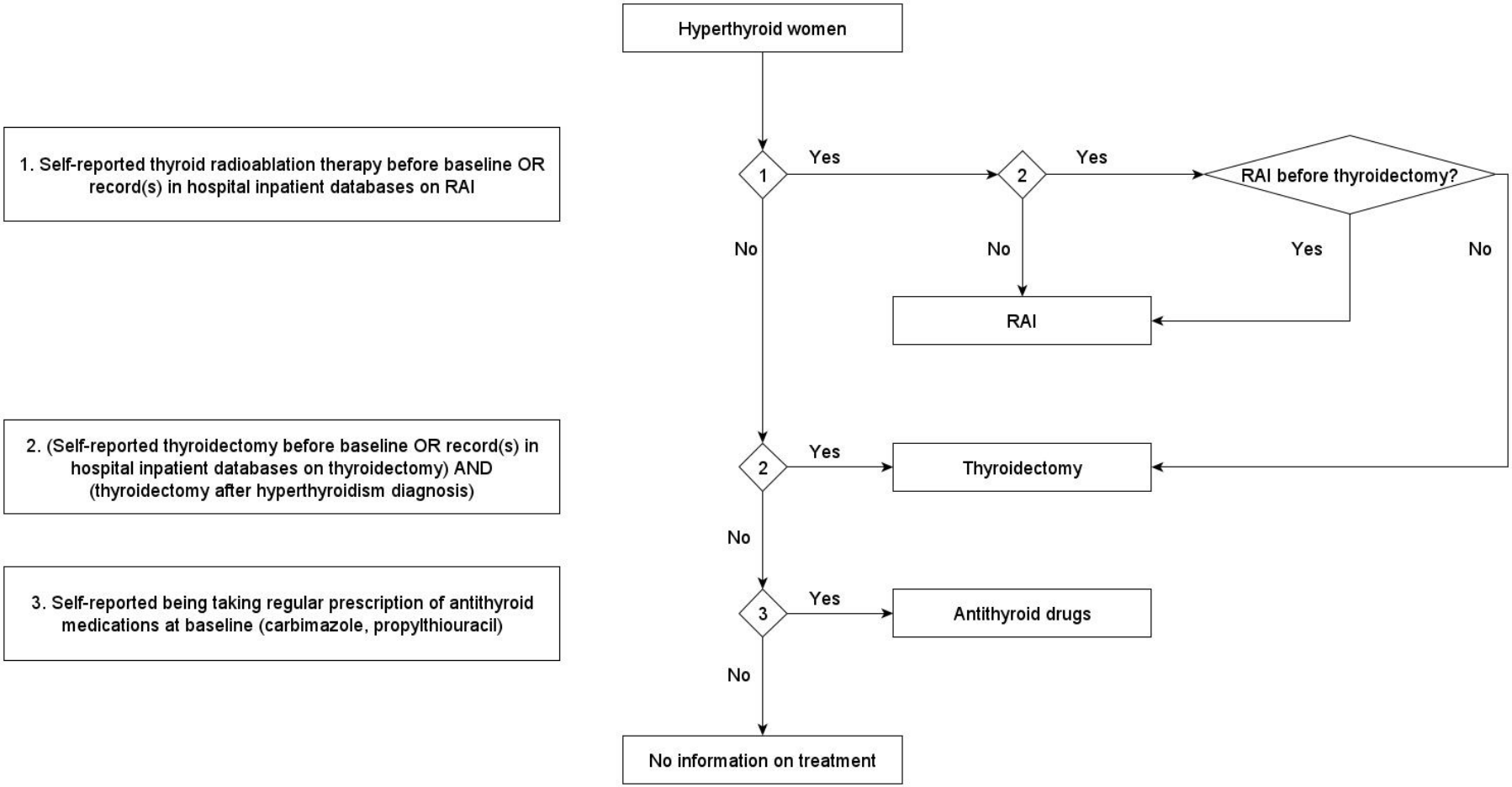


Figure 13 Definition of treatments for hyperthyroidism developed in the thesis

For more information:

- Self-report data on medical conditions, operations, and medications: https://biobank.ndph.ox.ac.uk/showcase/showcase/docs/Interview.pdf

- Hospital inpatient databases: https://biobank.ndph.ox.ac.uk/showcase/showcase/docs/HospitalEpisodeStatistics.pdf

IV.2.1.5 Statistical analyses

Model building

We used Cox proportional hazards models (Chapter III.1) to compute hazards ratios (HRs) and 95% confidence intervals (CIs) of breast cancer incidence according to thyroid dysfunction diagnosis and treatments. Time since baseline (i.e. UKB inclusion) was considered as the time scale. Proportional hazards assumptions were graphically evaluated based on plots of scaled Schoenfeld residuals against time, and tested by introducing an interaction term between thyroid dysfunction and follow-up time. No evidence of non-proportionality was found. We implemented the following model building strategy:

First, we fitted an age-adjusted Cox proportional hazards model for the association between thyroid dysfunction and breast cancer risk. We considered well-known risk factors of breast cancer as potential covariates, including menopausal hormone therapy, family history of breast cancer, parity and age at first birth, age at menarche, age at menopause, body mass index (BMI) , oral contraception, and physical activities. We included all potential covariates into the model and eliminated successively covariates that helped to increase the goodness-of-fit of the model, using AICs as an indicator. Additionally, for exploratory purposes, other factors, i.e alcohol consumption, ethnicity, smoking, mammography, Townsend score, were also tested as covariates. They did not increase the goodness-of-fit and were not included in the final model. The final list of covariates is composed of age at baseline (continuous), family history of breast cancer (yes/no), parity and age at first birth (No live birth/≥ one child, <30 years old at birth/≥ one child, ≥30 years old at birth/Unknown), menopausal status (premenopause/postmenopause before the age of 51/postmenopause after the age of 51), physical activities (Low/Moderate/High).

Assessment of confounding and modifying effects

The potential confounding effect was assessed by evaluating the age-adjusted associations with thyroid dysfunction, and changes in adjusted HRs for breast cancer risk exceeding 10% (114). Effect modification was evaluated by testing the statistical significance of an interaction term between thyroid dysfunction and the studied covariate [likelihood-ratio χ^2 tests for heterogeneity (categorical variables) and linear trend (continuous variables)]. When statistically significant multiplicative interactions were detected, we reported results for both additive and

multiplicative interactions (138).

Sensitivity analyses

We conducted several sensitivity analyses by:

(1) Assuming that hyperthyroid women with no information on treatments were treated with ATDs. Hyperthyroid patients are usually treated, the proportion of hyperthyroid women without information on treatment in the UKB cohort seemed too high to be considered as untreated individuals only. Meanwhile, ATDs are usually used as the first-line treatment for Graves' disease (the most common cause of hyperthyroidism) in the UK (32, 139). However, information on ATDs was more likely to be incomplete in the UKB cohort compared to that on surgery and RAI because only current medications were (self-)reported at baseline and the hospital databases that we used to collect follow-up information on treatments only contained information on surgery and RAI, not ATDs.

(2) Excluding women with other thyroid problems at baseline, e.g. thyroiditis and non-toxic goiter. Thyroidectomy can be used to treat other thyroid diseases and thyroid dysfunction could be a transient condition before other thyroid disorders.

(3) Conducting analyses stratified by the order of occurrence of hyper- and hypothyroidism, and excluding women who had hypothyroidism reported/recorded before hyperthyroidism or who had hyper- and hypothyroidism reported/recorded with unknown sequential order of occurrence to minimize misclassification.

(4) Analyzing separately thyroid dysfunction diagnoses and treatments recorded in the hospital databases only (likely reflecting the most severe conditions), and in self-reported data only to assess the impact of data sources on the results.

(5) Adding information on new thyroid dysfunction diagnoses and hyperthyroidism treatment identified in the hospital databases during follow-up, by considering exposure as a time-dependent variable.

(6) Excluding in-situ breast cancer diagnoses.

(7) Computing cause-specific hazard models (140) to consider death and non-breast cancer incidence as competing risks.

(8) Excluding women with missing data in the covariates used for adjustment.

IV.2.2 Systematic review and meta-analysis

This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (141). Our protocol was registered in the PROSPERO International prospective register of systematic reviews database (CRD42019125094) prior to the study.

IV.2.3 Search strategy

We performed a systematic literature search in PubMed/MEDLINE and the Cochrane library from inception to July 29, 2021. We included case-control and cohort studies that reported a measure of association between thyroid dysfunction (overt and subclinical) or thyroid hormone levels compatible with thyroid dysfunction diagnosed before cancer diagnosis and subsequent site-specific cancer risk. We restricted the search to English, French, and Vietnamese languages and studies in humans. Reference lists of eligible articles and previous systematic reviews (70, 72, 142-144) were hand-searched to identify additional relevant studies. In this thesis manuscript, we also included

IV.2.4 Study selection

One investigator (T.V.T.T) screened the title and abstract of all articles identified in the initial search and reviewed the full text of potentially eligible articles. Our exclusion criteria were (1) hyperthyroidism and hypothyroidism not reported separately, (2) no information on specific cancer sites, (3) no reported measure of association between hyperthyroidism or hypothyroidism, and cancer incidence, (4) thyroid dysfunction evaluated as a cancer biomarker (e.g. thyroid cancer), (5) thyroid dysfunction evaluated after cancer diagnosis or no/limited information on cancer history prior to thyroid dysfunction evaluation, (6) participants with a prior malignant condition or treated cancer and (7) transient thyroid dysfunction during pregnancy or severe illnesses.

IV.2.5 Data extraction and quality assessment

Using pre-defined data extraction forms, two investigators (T.V.T.T and N.J.) independently extracted the following information from the included studies: study setting and design, sample size, follow-up methods and duration, participant characteristics (age, sex, menopausal status), thyroid dysfunction (definition, ascertainment methods, treatments), cancer outcomes (definition, ascertainment methods), methods for statistical analysis (risk modeling, adjustment variables), and multivariable analysis results, including cases, control number and risk estimates. We retrieved data from the most informative studies in case of duplicate data sources.

T.V.T.T and N.J. independently assessed risk of bias of the included studies, using a modified Newcastle-Ottawa scale (NOS) (54). Inconsistent ratings between the two investigators were resolved by discussion.

IV.2.6 Statistical analysis

For each study, we extracted risk estimates (relative risk, odds ratio, hazard ratio, or standardized incidence ratio) adjusted for the most covariates and 95% confidence intervals (CI) from the original paper (Chapter III.2). Pooled risk ratios were estimated using DerSimonian and Laird random-effect models (145). In sensitivity analyses, we compared our results with those using fixed-effect models.

Heterogeneity across studies was evaluated using the Q-statistic with a conservative 10% p-value (146) and the I^2 statistic (147), with a value greater than 50% indicates a substantial heterogeneity level. To explore the heterogeneity sources, we conducted analyses stratified by thyroid dysfunction treatments: no treatment, radioactive iodine (RAI) only, thyroid hormone replacement therapy (THRT) only, mixed modalities, or unspecified treatments. No studies had investigated surgery and anti-thyroid drugs as a unique treatment of thyroid dysfunction. We analyzed only treatments ascertained at study inclusion due to the unavailability of follow-up data. Furthermore, we estimated pooled risk ratios stratified methods for thyroid dysfunction ascertainment (in-/out-patient hospital diagnoses, or others), study design (cohort or case-control), and geographic region (Asia, Australia, Europe, or North America). We also used the Q-statistic to test for subgroup differences - with p-values<0.1 indicating evidence of heterogeneity. Other sensitivity analyses were restricted to studies with low-to-moderate risk of bias for each NOS domain, or those with a minimum follow-up time of one year to minimize

the probability of reverse causation. We conducted an influence analysis by the leave-one-out method to assess whether the pooled risk estimates were driven by specific studies (148).

Publication bias was assessed by Egger tests and funnel plots (149). The analyses were performed in R version 3.5.3 (R Development Core Team, 2018) using the "*meta*" and "*metafor*" packages.

IV.3 Results

IV.3.1 Cohort study

IV.3.1.1 Population description

Among the 239,436 included women, the prevalence of baseline hyper- and hypothyroidism was 1.3% and 8.7%, respectively. Compared to women with no thyroid dysfunction, hyper- and hypothyroid women were likely to be older, postmenopausal, MHT and oral contraception ever user, obese/overweight, to have had a child at an earlier age, to have a lower level of physical activity, and more comorbidities at baseline (Table 10). During a median follow-up time of 7.1 years, 5,326 (2.2%) women were diagnosed with breast cancer.

IV.3.1.2 Hyperthyroidism

Overall, we found no statistically significant association between breast cancer risk and hyperthyroidism (Table 11), but the risk increased 5-10 years since hyperthyroidism diagnosis (HR=2.38, 95%CI 1.19-4.76). We also found an increased risk among women who were diagnosed with hyperthyroidism after the age of 60 years (HR=1.74, 95%CI 1.01-3.00), and among women with treated hyperthyroidism (HR=1.38, 95%CI 1.03-1.86). Stratification by treatment status showed that the increase of risk among women who were diagnosed with hyperthyroidism for 5-10 years or after the age of 60 years only concerned treated individuals, while there was no association among women with no information on treatment (133). These results did not substantially differ in sensitivity analyses (133). We found no confounding effect by comorbidities, and breast cancer risk factors.

When investigating potential effect modifiers, we found that the risk related to treated hyperthyroidism was higher among women menopaused at age >51 years (HR=2.07, 95%CI 1.33-3.22) than among women who had earlier menopause (HR= 1.18, 95%CI 0.76-1.83) or

were premenopausal at baseline (HR=0.79, 95%CI 0.30-2.11) (p-heterogeneity=0.09) (Table 12). Among all the factors investigated, the menopausal status/age at menopause and history of hypertension (based on very few cases) were the only modifying effects that we detected (Figure 14). These results did not vary after adjustment for age at menopause as a continuous variable (for postmenopausal women), or in further analyses stratified by age at baseline, natural or artificial menopause, age at / time since hypothyroidism diagnosis, occurrence of thyroid dysfunction before or after menopause, or use of MHT or not.

IV.3.1.3 Hypothyroidism

We found no statistically significant association between hypothyroidism and breast cancer risk overall (HR=0.93, 95%CI 0.84-1.02), or after stratification by calendar year at diagnosis or treatment status (Table 13). However, there was a decreased risk of breast cancer among women diagnosed with hypothyroidism before the age of 40 years (HR=0.71, 95%CI 0.54-0.94) or diagnosed for hypothyroidism for more than 10 years (HR=0.85, 95%CI 0.74-0.97), compared to women with no thyroid dysfunction. The results did not substantially differ in sensitivity analyses (133). There was no confounding effect by comorbidities, and breast cancer risk factors.

Among all the factors investigated, the only modifying effect that we detected was the menopausal status/age at menopause (Figure 14). We observed lower risks among premenopausal women at baseline (HR=0.69, 95%CI 0.51-0.93) or women menopaused at ages ≤51 years (HR=0.90, 95%CI 0.79-1.02) compared to those with later menopause (HR=1.10, 95%CI 0.93-1.30) (p-value for heterogeneity: 0.017) (Table 14). These results did not vary after adjustment for age at menopause as a continuous variable (for postmenopausal women), or in further analyses stratified by age at baseline, natural or artificial menopause, age at / time since hypothyroidism diagnosis, occurrence of thyroid dysfunction before or after menopause, or use of MHT or not.

Table 10 Baseline characteristics of the study population

	No thyroid dysfunction reported (n=217,451)	Hyperthyroidism (n=3,227)[1]	P-value[2]	Hypothyroidism (n=20,762)[1]	P-value[2]
Person-years of follow-up, median (IQR)	7.1 (6.4, 7.8)	7.1 (6.4, 7.8)	0.377	7.0 (6.4, 7.8)	< 0.001
Age at baseline, Mean (SD)	56.4 ± 8.1	58.0 ± 7.6	<0.001	58.9 ± 7.3	<0.001
Menopause status, n (%)			<0.001		<0.001
Still had periods	60,047 (27.6)	612 (19.0)		3,189 (15.4)	
Had menopause before the age of 51	106,860 (49.1)	1,764 (54.7)		12,105 (58.3)	
Had menopause after the age of 51	50,544 (23.2)	851 (26.4)		5,468 (26.3)	
Age at menopause[3], Mean (SD)	49.3 ± 5.1	49.2 ± 5.4	0.918	49.0 ± 5.5	< 0.001
Age at menarche, Mean (SD)	13.0 ± 1.6	12.9 ± 1.6	0.213	12.9 ± 1.6	<0.001
Family history of breast cancer, n (%)	22,951 (10.6)	309 (9.6)	0.077	2,113 (10.2)	0.093
Ever use of menopausal hormone therapy[3], n (%)			<0.001		<0.001
No	77,660 (49.3)	1,193 (45.6)		7,473 (42.5)	
Yes, for less than 5 years	27,624 (17.5)	442 (16.9)		3,206 (18.2)	
Yes, for more than 5 years	41,604 (26.4)	764 (29.2)		5,384 (30.6)	
Yes, unknown duration	9,723 (6.2)	206 (7.9)		1,432 (8.1)	
Unknown	793 (0.5)	10 (0.4)		78 (0.4)	
Ever use of oral contraception, n (%)			<0.001		<0.001
No	39,784 (18.3)	723 (22.4)		4,722 (22.7)	
Yes, for less than 10 years	78,956 (36.3)	1,216 (37.7)		7,855 (37.8)	
Yes, for more than 10 years	78,019 (35.9)	972 (30.1)		6,070 (29.2)	
Yes, unknown duration	20,338 (9.4)	308 (9.5)		2,078 (10.0)	
Unknown	354 (0.2)	8 (0.2)		37 (0.2)	
Parity and age at first birth, n (%)			<0.001		<0.001
No live birth	41,026 (18.9)	567 (17.6)		3,336 (16.1)	
≥ one child, <30 years old at birth	135,291 (62.2)	2,134 (66.1)		14,340 (69.1)	
≥ one child, ≥30 years old at birth	40,071 (18.4)	516 (16.0)		3,007 (14.5)	
Unknown	1,063 (0.5)	10 (0.3)		79 (0.4)	

Corpulence, n (%)			0.024		<0.001
Obesity/Overweight, BMI ≥25 kg/m²	128,257 (59.0)	1,974 (61.2)		14,564 (70.1)	
Normal weight/Underweight, BMI <25 kg/m²	88,047 (40.5)	1,239 (38.4)		6,107 (29.4)	
Unknown	1,147 (0.5)	14 (0.4)		91 (0.4)	
Comorbidities, n (%)			<0.001		<0.001
Type 2 diabetes	6,534 (3.0)	166 (5.1)		1,203 (5.8)	
Hypertension	49,848 (22.9)	1,006 (31.2)		6,579 (31.7)	
Depression	15,145 (7.0)	263 (8.1)		2,027 (9.8)	
Autoimmune diseases	20,263 (9.3)	450 (13.9)		2,851 (13.7)	
Levels of physical activities, n (%)			0.002		<0.001
Low	68,804 (31.6)	1,106 (34.3)		7,438 (35.8)	
Moderate	77,862 (35.8)	1,146 (35.5)		7,084 (34.1)	
High	70,785 (32.6)	975 (30.2)		6,240 (30.1)	

BMI: Body-mass index

[1] Women with both hyper- and hypothyroidism reported/recorded (n=2,004) contributed to both columns of hyper- and hypothyroidism

[2] P-value of t-test, Mann-Whitney U test, and $\chi 2$ test, where appropriate

[3] Postmenopausal women only

Table 11 Hazard ratios of breast cancer incidence associated with hyperthyroidism diagnosis and treatment versus no thyroid dysfunction at baseline

	Hyperthyroidism		
Characteristics	**No. of breast cancer cases/Person-years**	**HR**	**95%CI**
No thyroid dysfunction (reference)	4,854/1,518~~670	**1**	**—**
Overall	79/22,520.6	1.08	0.86, 1.35
Age at diagnosis			
Before 40 years old	20/8,436.4	0.75	0.48, 1.16
Between 40-60 years old	45/11,725	1.18	0.88, 1.58
After 60 years old	13/2,007.2	**1.74**	**1.01, 3.00**
Unknown age at diagnosis	1/352	0.92	0.13, 6.56
P-trend[1]			*0.145*
Time since diagnosis			
Less than 5 years ago	4/2,333.6	0.70	0.26, 1.87
Between 5-10 years ago	25/4,947.4	**1.58**	**1.06, 2.33**
More than 10 years ago	49/14,887.6	0.97	0.73, 1.29
Unknown time at diagnosis	1/352	0.91	0.13, 6.47
P-trend[1]			*0.124*
Calendar year at diagnosis			
Before 1990	26/6,910.3	1.09	0.74, 1.61
1990-2000	14/5,946.9	0.74	0.44, 1.24
After 2000	38/9,317.3	1.29	0.94, 1.77
Unknown time at diagnosis	1/346.2	0.93	0.13, 6.60
P-trend[1]			*0.366*
Treatment status			
Without information on treatment (1)	35/12,816.1	0.84	0.60, 1.17
With information on treatment	44/9,704.5	**1.38**	**1.03, 1.86**
Types of hyperthyroidism treatment			
Antithyroid medications (2)	9/1,978	1.46	0.76, 2.81
RAI (3)	11/2,697.4	1.23	0.68, 2.23
Surgery (4)	24/5,029.1	1.44	0.96, 2.15
(1) or (2)	44/14,794.1	0.92	0.68, 1.24
(3) or (4)	35/19,822.2	1.37	0.98, 1.91
Time since hyperthyroidism treatment			
Less than 5 years ago	1/435.2	0.97	0.14, 6.90
Between 5-10 years ago	8/1,068.6	**2.38**	**1.19, 4.76**
More than 10 years ago	26/6,192.9	1.24	0.84, 1.82
Unknown time at diagnosis	9/2,007.8	1.43	0.74, 2.74
P-trend[1]			*0.044*

HR = Hazard Ratio, CI = Confidence Interval, RAI: Radioactive iodine therapy

[1] p-trend was calculated after excluding hyperthyroidism/hypothyroidism with unknown time at diagnosis/treatment

Table 12 Breast cancer risk associated with treated hyperthyroidism according to baseline menopausal status and age at menopause

Menopausal status and age at menopause	N with/without breast cancer	HR (95% CI)	HR (95% CI) within strata of menopausal status and age at menopause
Premenopause			
No thyroid dysfunction	1,194/58,853	1.19 (1.07-1.31), P = 0.001	1.00
Treated hyperthyroidism	4/248	0.91 (0.34-2.44), P = 0.856	0.77 (0.29-2.05), P = 0.601
Having menopause before the age of 51			
No thyroid dysfunction	2,341/104,519	1.00	1.00
Treated hyperthyroidism	20/743	1.19 (0.76-1.84), P = 0.443	1.19 (0.76-1.84), P = 0.443
Having menopause after the age of 51			
No thyroid dysfunction	1,319/49,225	1.16 (1.08-1.24), P < 0.001	1.00
Treated hyperthyroidism	20/358	2.39 (1.54-3.71), P < 0.001	2.07 (1.33-3.22), P = 0.001

Measure of effect modification of premenopause on additive scale: Treated hyperthyroidism: RERI (95% CI) = -0.46 (-1.5-0.58), P = 0.391

Measure of effect modification of having menopause after the age of 51 on additive scale: Treated hyperthyroidism: RERI (95% CI) = 1.05 (-0.12-2.22), P = 0.08

Measure of effect modification of premenopause on multiplicative scale: Treated hyperthyroidism: ratio of HRs (95% CI) = 0.65 (0.22-1.9), P = 0.429

Measure of effect modification of having menopause after the age of 51 on multiplicative scale: Treated hyperthyroidism: ratio of HRs (95% CI) = 1.74 (0.93-3.25), P = 0.081

HRs are adjusted for age at baseline (continuous), family history of breast cancer (yes/no), parity and number of live birth (No live birth/≥ one child, <30 years old at birth/≥ one child, ≥30 years old at birth/Unknown), and physical activities (Low/Moderate/High)

Table 13 Hazard ratios of breast cancer incidence associated with hypothyroidism diagnosis and treatment versus no thyroid dysfunction at baseline

	Hypothyroidism		
Characteristics	**No. of breast cancer cases/Person-years**	**HR**	**95%CI**
No thyroid dysfunction (reference)	4,854/1,518~~670	1	—
Overall	442/144,213.1	0.93	0.84, 1.02
Age at diagnosis			
Before 40 years old	50/23,615.7	**0.71**	**0.54, 0.94**
Between 40-60 years old	271/87,945.4	0.94	0.83, 1.06
After 60 years old	70/16,728.3	1.11	0.88, 1.41
Unknown age at diagnosis	51/15,923.6	0.97	0.73, 1.27
P-trend[1]			*0.452*
Time since diagnosis			
Less than 5 years ago	34/15,154.9	0.91	0.65, 1.27
Between 5-10 years ago	131/37,024.4	1.08	0.91, 1.29
More than 10 years ago	226/76,110.1	**0.85**	**0.74, 0.97**
Unknown time at diagnosis	51/15,923.6	0.99	0.75, 1.30
P-trend[1]			*0.872*
Calendar year at diagnosis			
Before 1990	47/17,558.6	0.79	0.59, 1.05
1990-2000	120/40,954.8	0.88	0.73, 1.05
After 2000	224/69,814.3	0.99	0.86, 1.13
Unknown time at diagnosis	51/15,885.4	0.96	0.73, 1.27
P-trend[1]			*0.352*
Treatment status			
Without information on treatment (1)	22/4,831.6	1.39	0.91, 2.11
With information on treatment	420/139,381.5	0.91	0.83, 1.01

HR = Hazard Ratio, CI = Confidence Interval

[1] p-trend was calculated after excluding hyperthyroidism/hypothyroidism with unknown time at diagnosis/treatment

HRs are adjusted for age at baseline (continuous), family history of breast cancer (yes/no), parity and number of live birth (No live birth/≥ one child, <30 years old at birth/≥ one child, ≥30 years old at birth/Unknown), menopausal status (premenopause/postmenopause before the age of 51/postmenopause after the age of 51), physical activities (Low/Moderate/High)

Table 14 Breast cancer risk associated with hypothyroidism according to baseline menopausal status and age at menopause

Menopausal status and age at menopause	N with/without breast cancer	HR (95% CI)	HR (95% CI) within strata of menopausal status and age at menopause
Premenopause			
No thyroid dysfunction	1194/5,885 3	1.19 (1.08-1.32), P = 0.001	1.00
Hypothyroidism	44/3,145	0.82 (0.61-1.12), P = 0.214	0.69 (0.51-0.93), P = 0.016
Having menopause before the age of 51			
No thyroid dysfunction	2341/104,519	1.00	1.00
Hypothyroidism	240/11865	0.90 (0.79-1.02), P = 0.109	0.90 (0.79-1.02), P = 0.109
Having menopause after the age of 51			
No thyroid dysfunction	1319/4,922 5	1.15 (1.08-1.24), P < 0.001	1.00
Hypothyroidism	158/5,310	1.27 (1.08-1.49), P = 0.004	1.10 (0.93-1.30), P = 0.261

Measure of effect modification of premenopause on additive scale: Hypothyroidism: RERI (95% CI) = -0.26 (-0.55-0.02), P = 0.066

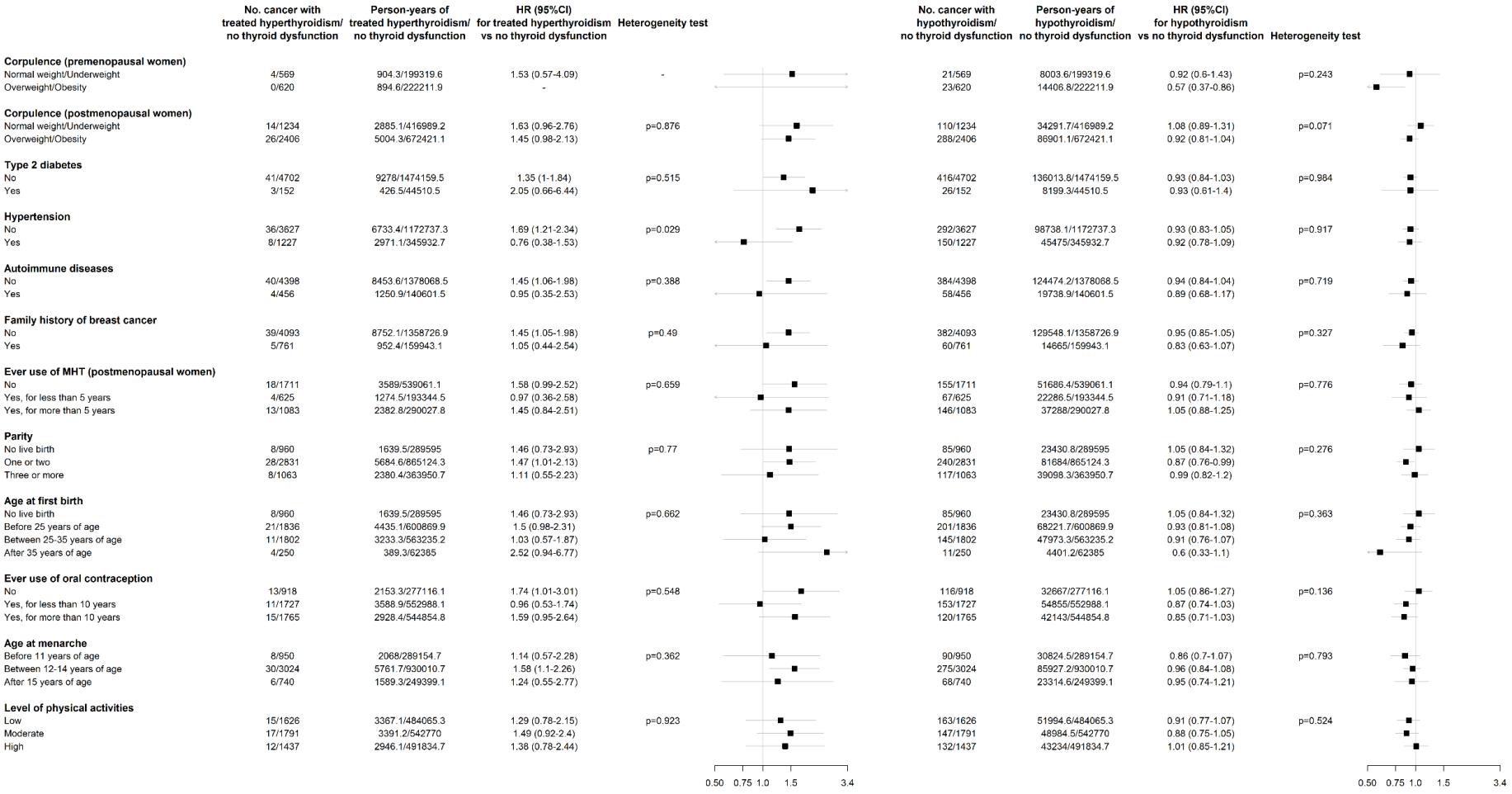
Measure of effect modification of having menopause after the age of 51 on additive scale: Hypothyroidism: RERI (95% CI) = 0.22 (-0.02-0.46), P = 0.073

Measure of effect modification of premenopause on multiplicative scale: Hypothyroidism: ratio of HRs (95% CI) = 0.77 (0.55-1.07), P = 0.121

Measure of effect modification of having menopause after the age of 51 on multiplicative scale: Hypothyroidism: ratio of HRs (95% CI) = 1.23 (0.99-1.51), P = 0.06

HRs are adjusted for age at baseline (continuous), family history of breast cancer (yes/no), parity and number of live birth (No live birth/≥ one child, <30 years old at birth/≥ one child, ≥30 years old at birth/Unknown), and physical activities (Low/Moderate/High)

Figure 14 Evaluation of effect modification of comorbidities, and breast cancer risk factors in the association between thyroid dysfunction and breast cancer risk.



Results for “Unknown” category were not shown. HR: Hazard ratio, CI: Confidence interval

IV.3.2 Systematic review of all available evidence in the literature and meta-analysis combining our results with comparable other studies

After screening the title and abstract of 3,287 non-duplicated articles and reviewing the full text of 151 potentially eligible articles, we included 14 studies (11 cohort, and 3 case-control studies) on breast cancer risk in the literature synthesis, including our study in the UKB cohort (Figure 15). Of these, 13 studies contributed to the meta-analysis for breast cancer.

IV.3.2.1 Study characteristics

Studies were conducted in Europe (n=6), the USA (n=4), Taiwan (n=2), Korea (n=1) and Australia (n=1). Six studies were population-based (133, 150-154), of which three were nationwide (133, 151, 152, 154), where thyroid dysfunction was assessed through in- and/or out-patient hospital databases (Table 15). Two population-based studies had information on serum TSH and/or thyroid hormones concentrations (150, 153). Differences in study design resulted in widely variable sample size (ranging from 342 to 239,436), and mean/median follow-up time (ranging from 5 to 17 years on average; not reported for 8 studies). Seven studies included both females (proportion: 56% to 90%) and males. In cohort studies, the prevalence of hyperthyroidism and hypothyroidism ranged respectively from 0.3% to 2.5% and 0.6% to 14.7% across cohorts, respectively (mean age at thyroid dysfunction assessment: 40 to 64 years). Treatment modalities of thyroid dysfunction were: RAI only (155), THRT only (74, 156), mixed modalities (133, 157, 158), no treatment (65, 150, 153), or unspecified (74, 151, 152, 154, 159). Treatments were ascertained at study inclusion since there was incomplete (157) or no follow-up data in the original studies. Diabetes and overweight/obesity were the most common reported comorbidities, with a prevalence of 2-23.5% in cohorts and 10-46% in case-control studies. Overall, nine (64%) studies were considered as moderate-to-low risk of bias (Appendix 5). Neither the funnel plots nor the Egger's test showed evidence of publication bias.

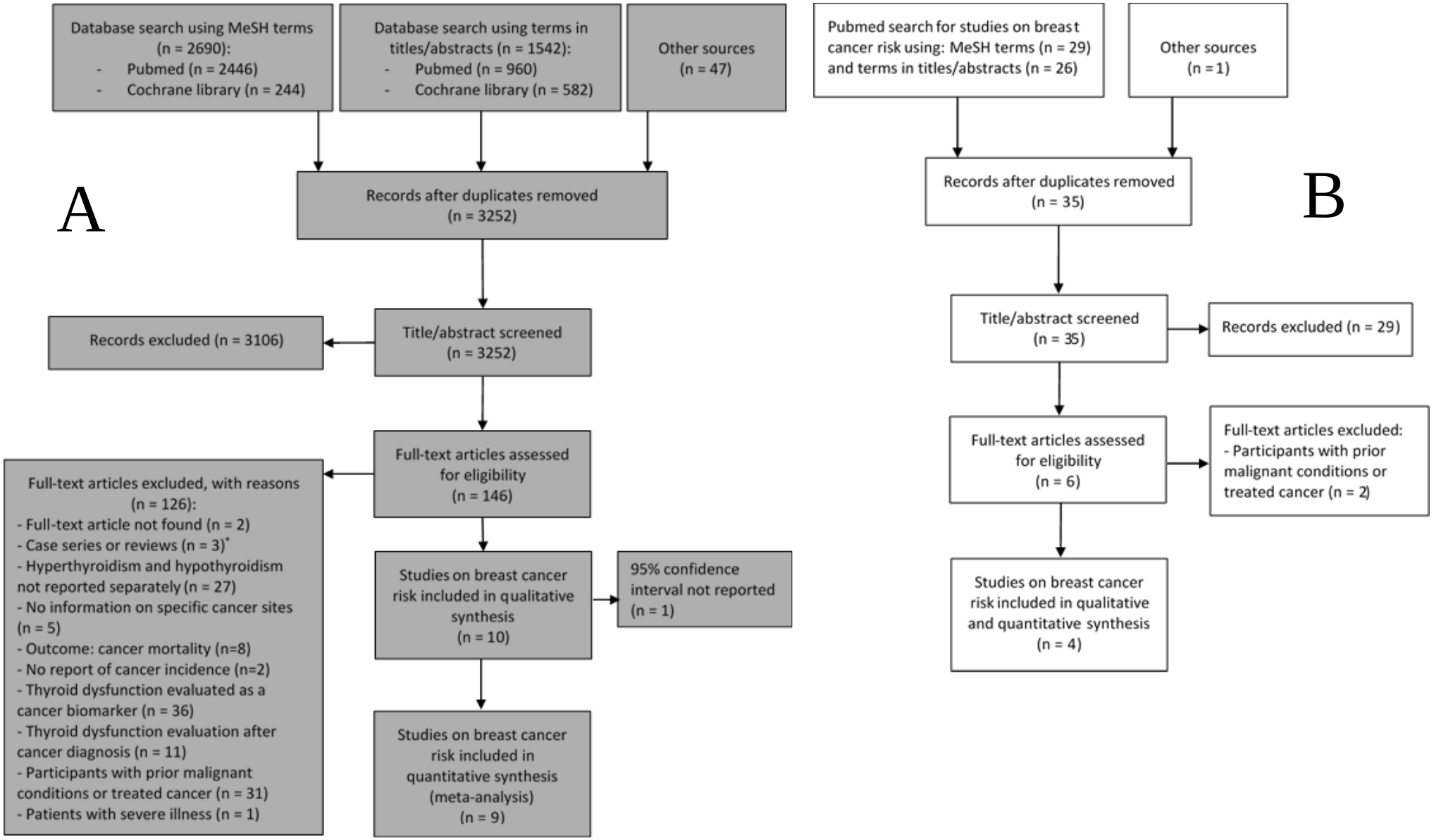


Figure 15 PRISMA FlowDiagram Outlining Search Strategy and Final Included and Excluded Studies.

A: FlowDiagram in the original systematic review and meta-analysis. B: FlowDiagram in the Pubmed search for studies on breast cancer incidence published from January 29, 2019 to July 29, 2021

Table 15 Characteristics of 10 studies included in the systematic review that reported breast cancer risk associated with thyroid dysfunction

Ref.	Country	Study design	Methods of follow-up and cancer ascertainment	Follow-up time in years: mean/median (min-max)[1]	Size of study population	Age in years: mean /median (min-max)	% Women	% Post-menopausal (women)	Thyroid dysfunction			Statistic analysis	Covariates in multivariate analysis[2]
									Definition	Method of ascertainement	Treatment(s) (%)		
Studies included in the original systematic review and meta-analysis													
Munoz, 1978	USA	Hospital-based cohort	Hospital medical records (2 centers)	13.8/nr (0.1-nr)	N=342	Nr	80.7	Nr	Hyperthyroidism : Graves' disease	Medical/laboratory reports	Desiccated thyroid, levothyroxine, thyroidectomy, radioactive iodine, Lugol's iodine, antithyroid drugs	SIR	Age, sex
Goldman, 1988	USA	Single-institution, hospital-based cohort	Cooperative Thyrotoxicosis Therapy Follow-up Study, hospital medical records, administrative databases (vital status), self-reported questionnaire	17/nr (1-33)	1762	47/nr (nr-nr)	100.0	Nr	Treated hyperthyroidism	Hospital medical records, self-reported questionnaire, physical exams	Radioactive iodine (n=1406), surgery (n=573), antithyroid drugs (n=1069) - combinations of these treatments were possible	SMR, SIR	Mortality analysis: Age, calendar time Incidence analysis: Age, calendar time, race
Mellemgaard, 1998	Denmark	National cohort	National civil registration system, national cancer registry	Nr/nr (1-15)	N=nr	Nr/nr (0-100+) (64% >50 years of age)	84.4 (among exposed patients)	Nr	Hyperthyroidism : Thyroitoxicosis (ICD-8-CM code: 242)	National insurance database: in-patient claims	Nr	SIR	Age, sex, calendar time
Metso, 2007	Finland	Hospital-based cohort	National population registry, national cancer registry	10/nr (0.1-39)	N=5,586	Nr/62 (IQR 50-75)	83.6	Nr	Hyperthyroidism treated with RAI (Graves' disease: 57%, toxic multinodular goiter or adenoma, 43%)	Hospital medical records	Radioactive iodine (100%), mean cumulative dose =305 MBq (range: 55-2,664 MBq)	Mantel-Haenszel's incidence rate ratios	Age, sex
Hellevik, 2009	Norway	Population-based cohort	National cancer registry	Nr/9 (0-10)	29,691	Nr/nr (20-nr)	66.4	Nr	Hyperthyroidism[3]: TSH<0.50 mU/L; Hypothyroidism[3]: TSH≥3.6 mU/L;	Baseline blood test (DEFLFIA from Wallac Oy[4])	None	Cox proportional hazards regression model	Age, sex, smoking status

[1] Until otherwise specified, follow-up time was determined as following: For cohort studies, the time on study, considered from the date of the thyroid dysfunction evaluation to the date of cancer diagnosis or end of follow-up; for case-control studies: the period when participants were diagnosed with thyroid dysfunction in the past before cancer diagnosis

[2] For main analysis

[3] TSH reference range in the analysis: Chan, 2017 – 0.4-4.0 mU/L, Hellevik, 2009 – 0.5-1.4 mU/L, Huang, 2017 – 1.2-1.93 mU/L, Mondul, 2012 – 0.3-3 mU/L

[4] DELFIA hTSH Ultra: sensitivity, 0.03 mU/L; and total analytic variation, <5%

									No self-reported thyroid disease (types: nr)				
Chen, 2013 (1)	Taiwan	National cohort	National insurance database (histological confirmation)	Nr/nr (0-14)	25,125	42/nr (20-100+)	77.3	Nr	Hyperthyroidism : Graves' disease (ICD-9-CM code: 242.0)	National insurance database: ≥3 in- and out-patient claims	Thyroidectomy (0.14%): not used for analysis	Poisson regression model, Cox proportional hazards regression model	Age, sex, diabetes, hypertension, hyperlipidemia
Chen, 2013 (2)	Taiwan	National cohort	National insurance database (histological confirmation)	Nr/nr (0-13)	7,605	40/nr (0-100+)	90.1	Nr	Hypothyroidism: Hashimoto's thyroiditis (ICD-9-CM code: 245.2)	National insurance database: in- and out-patient claims	Nr	Poisson regression model, Cox proportional hazards regression model	Age, sex, diabetes, hypertension, hyperlipidemia, heart disease
Chan, 2017	Australia	Population-based cohort	Regional cancer and death registries	Nr/nr (2-20)	3,649	51/nr (25-84)	55.5	52.1	Subclinical hyperthyroidism[3]: TSH<0.4 mU/L and FT4 <21.2 pmol/L; Subclinical hypothyroidism[3] : TSH>4 mU/L and FT4 >12.6 pmol/L	Baseline blood test (third generation assay)	No thyroid-related medications at baseline (thyroxine supplementation, anti-thyroid medications, lithium, amiodarone, carbamazepine or phenytoin use)	Cox proportional hazards regression model	Age, sex, marital status, occupation, smoking, alcohol consumption, physical activities, BMI, diabetes, menopausal status, oral contraceptive use or MHT use
Talamini, 1997	Italy	Hospital-based case-control	Hospital records (histological confirmation)	Nr/nr (0-nr)	N=5,157	Nr/56 (20-74)	100.0	64.5	Hyperthyroidism, hypothyroidism	Structured interview (wihin the year after cancer diagnosis)	Nr	Logistric regression models	Age, study area, education, parity, BMI quintiles, menopausal status
Cristofanilli, 2005	USA	Cancer screening center-based case-control	Hospital records (1 center)	Nr/nr (0-nr)	N=2,224	51/nr (nr-nr)	100.0	63.7	Treated primary hypothyroidism	Self-reported questionnaire (blinded to case/control status)	Thyroid hormone replacement, e.g. Levothyroxine (100%)	Unconditional logistic regression model	Age, first degree family history of breast cancer, history of pregnancy, use of MHT, menopausal status
Studies recently published (from 29/01/2019-29/07/2021 other than our study in the UKB													
Kim, 2019	Korea	Cancer screening cancer-based cohort	Self-report	Nr/4.8 (nr-nr)	N=62,546	46.0/nr (40-nr)	100.0	30.9	(Subclinical and overt) Hyperthyroidism: TSH<0.25 µlU/ml; (subclinical and overt) hypothyroidism: TSH>5.0 µlU/ml	Baseline blood test	No thyroid-related medications at baseline	Cox proportional hazards regression model	Age, center, year of screening exam, smoking status, regular exercise, alcohol intake, education level, BMI, history of diabetes, history of hypertension, history of cardiovascular disease, family history of breast cancer, female hormone medication and menopause
Weng, 2020	USA	Cohort	Self-reported questionnaire, medical records and pathology reports	Nr/nr (0-nr)	N=134,122	62.8-63.9/nr (50-79)	100.0	100.0	Hyperthyroidism, hypothyroidism	Self-report at baseline	Hyperthyroidism medication (2.7%)	Cox proportional hazards regression model	Age, race/ethnicity, body mass index, smoking, alcohol intake, duration of menopausal hormone replacement therapy, history of

												hysterectomy/oophorectomy, parity history and numbers, age at menarche, age at menopause, family history of breast cancer, mammogram ever, and breastfeeding
Tran, 2021	UK	Population-based cohort	Cancer registries	7.0/7.0 (1-10)	N=239,436	57/58 (40-71)	100.0	73.5	Hyperthyroidism, hypothyroidism	Self-report conditions and medications, hospital inpatient databases	Hyperthyroidism: Thyroidectomy, medications, radioactive iodine; Hypothyroidism: thyroid hormone replacement therapy	Cox proportional hazards regression model	Age at baseline, menopausal status, family history of breast cancer, parity and age at first birth, and level of physical activity
Bach, 2020	UK	Case-control (data from 200 general practices)	Cancer diagnosis in general practices	Nr/nr (1-nr)	N=14,816	58.4/nr (18-80)	100.0	nr	Hyperthyroidism, hypothyroidism	Diagnosis in general practices	nr	Logistic regression model	Age, body-mass index, hormones replacement therapy, and physician

IV.3.2.2 Main results

Risk of breast cancer associated with hyperthyroidism or hypothyroidism was investigated in eleven (65, 74, 133, 150, 151, 153-155, 157, 159, 160) (N=66,216) and nine (65, 74, 133, 150, 151, 153, 156, 159, 160) (N=26,572) studies, respectively. Most studies had a low to moderate risk of bias in terms of participants' selection and exposure/outcome ascertainment. However, except in five studies (65, 74, 133, 150, 156), no adjustment was made for potential confounders such as hormone replacement therapy/menopausal status, parity, or family history of breast cancer. Except for one study reporting only one cancer case among the exposed (150), all other studies reported statistically significant (151, 155) or non-significant (65, 74, 133, 153, 154, 157, 159, 160) increased risks with hyperthyroidism (Figure 16). In contrast, most studies found decreased risks with hypothyroidism, though they mostly reported statistically non-significant associations (Figure 16). This decrease was statistically significant in only two large studies after adjustment for important potential confounders such as family history of breast cancer, hormone replacement therapy, and menopausal status (74, 156).

The pooled risk ratio was 1.15 (95%CI: 1.06 to 1.24, 890 cases among the exposed) for hyperthyroidism, with weak evidence of heterogeneity (I^2=0%, p=0.49), and 0.86 (95%CI 0.75 to 0.98, 2,427 cases among the exposed) for hypothyroidism, but with a substantial degree of heterogeneity (I^2=75%, p<0.01). However, in the influence analyses, when excluding the study which showed the most markedly lower risk of breast cancer among hypothyroid women (161), the degree of heterogeneity in the hypothyroidism analysis was moderate (I^2=32%, p=0.17) and the pooled risk estimate remained consistent (RR=0.94, 95%CI 0.87-1.01). When doing the influence analysis with the other studies, the risk estimates were relatively consistent, and most influential studies accounted for important breast cancer risk factors (74, 133) (Appendix 5: Supplementary figure 3). The only study reporting a positive association with hypothyroidism had no information on potential confounders (162).

The risk ratio associated with hyperthyroidism was slightly higher among women treated with RAI only (risk ratio = 1.54, 95%CI 1.08 to 2.19) (155) than in untreated women (risk ratio = 1.22, 95%CI 0.74 to 2.00) (65, 150, 153) and populations treated with different/unreported treatments (risk ratio = 1.13, 95%CI 1.04 to 1.22) (74, 78, 133, 159, 160, 163, 164). Nevertheless, the difference by different treatment subgroups was not statistically significant ($p_{heterogeneity}$=0.44). Breast cancer risk did not vary whether among women treated with THRT

(risk ratio = 0.65, 95%CI 0.31 to 1.35) (133, 156), or untreated women (risk ratio = 0.80, 95%CI 0.60 to 1.07) (65, 150, 153) ($p_{heterogeneity}$ among treatment subgroups=0.34).

In studies with available information on menopausal status (65, 74, 133, 159), the pooled risk ratio associated with hyperthyroidism was higher among postmenopausal women risk ratio = 1.12, 95%CI 0.97 to 1.29) than in premenopausal women (risk ratio = 0.87, 95%CI 0.59 to 1.30). However, the difference by menopausal status subgroups was not statistically significant ($p_{heterogeneity}$=0.24). In contrast, breast cancer risk significantly lower among premenopausal women with hypothyroidism (risk ratio = 0.69, 95%CI 0.53 to 0.89) than among postmenopausal women (risk ratio = 0.92, 95%CI 0.80 to 0.97) ($p_{heterogeneity}$=0.03)

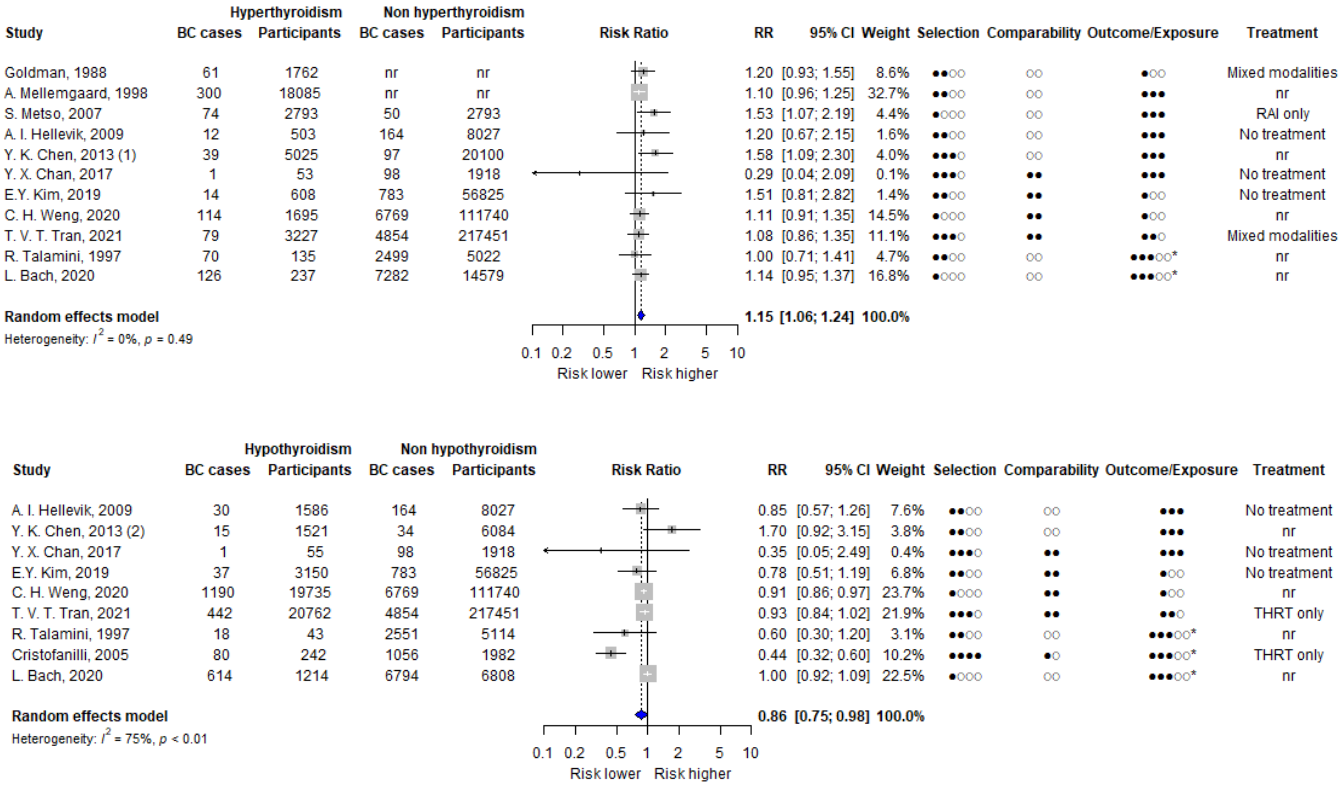


Figure 16 Forest plots for the association between hyper- or hypothyroidism and the risk of breast cancer.

The overall risk ratios are displayed as diamonds. The size of each square is proportional to the weight of the study. CI: confidence interval; nr: not reported; PY: person-year; RAI: radioactive iodine; RR: risk ratio. *Case-control studies. Metso et al., 2007: results estimated based on a figure reporting the primary results of the article, exact results were not available.

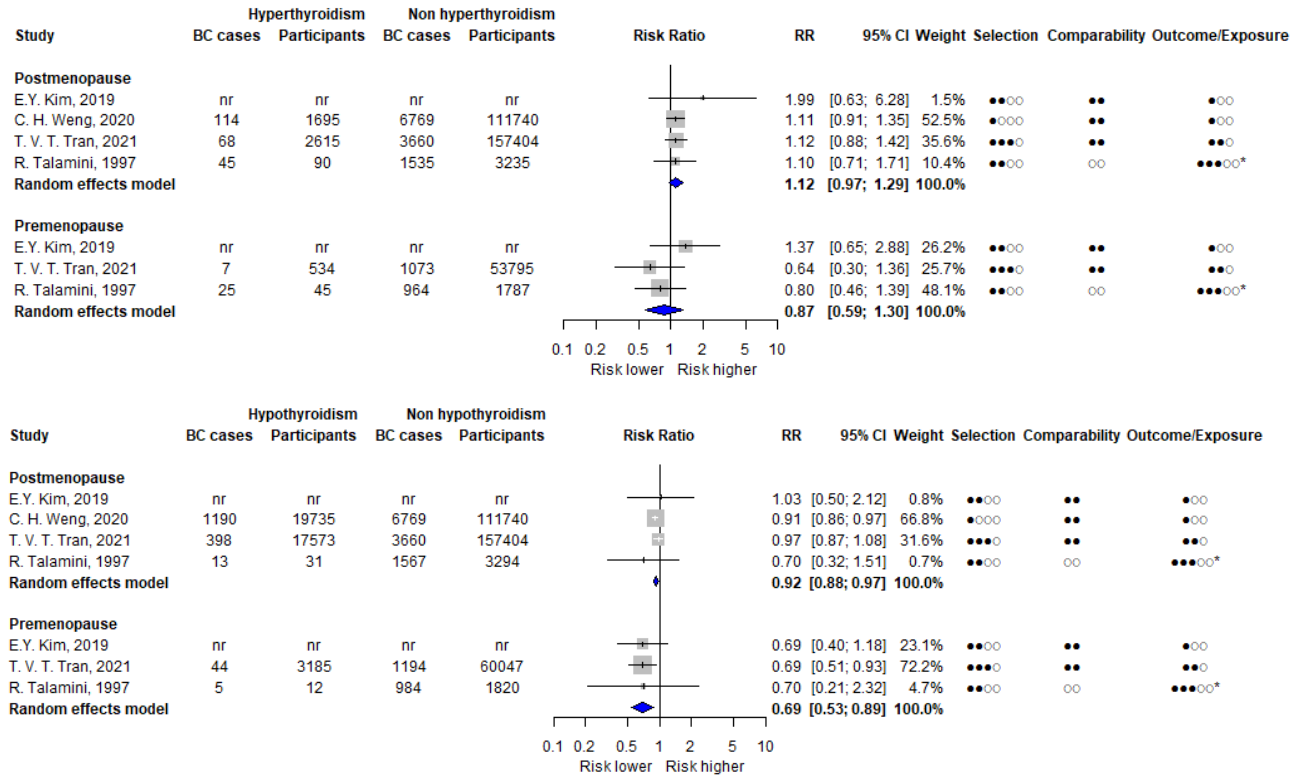


Figure 17 Forest plots for the association between hyper- or hypothyroidism and the risk of breast cancer according to menopausal status.

The overall risk ratios are displayed as diamonds. The size of each square is proportional to the weight of the study. CI: confidence interval; nr: not reported; PY: person-year; RAI: radioactive iodine; RR: risk ratio

IV.3.2.3 Sensitivity and subgroup analyses

No substantial difference in the estimated risk ratios was observed between random- and fixed-effect models. The higher risk of breast cancer associated with hyperthyroidism did not change when including only studies with available risk estimates after at least one year of follow-up (78, 133, 150, 160, 163, 164) (Appendix 5: Supplementary figure 4). For all exposure groups, cohorts yielded higher risk ratios than case-control studies. The pooled risk ratios were also higher in studies where thyroid dysfunction was assessed through hospital or health insurance databases compared to studies using blood measurements or self-reported data. Subsequently, studies conducted in Europe reported the smallest risk estimates for all outcomes, while those conducted in Asia yielded the highest risk estimates. However, pooled risk ratios did not statistically differ among regions. Other sensitivity, subgroup, and influence analyses did not substantially modify the results.

IV.4 Discussion

Main findings from the cohort analysis

In this chapter, we describe two sets of analyses to examine the association between thyroid dysfunction and breast cancer risk. First, our analysis of the UKB cohort showed no significant evidence that ever having thyroid dysfunction overall is associated with the incidence of female breast cancer. There were only statistically significant findings in support of an increased risk of breast cancer among women treated for hyperthyroidism and a decreased risk among those who had been diagnosed with hypothyroidism for more than 10 years or before the age of 40. Our cohort study lends support for the hypothesis of a more pronounced association between thyroid hormone levels and breast cancer risk among women with late menopause.

Second, in a systematic review and meta-analysis of published studies plus the UKB cohort, ever having hyper- and hypothyroidism were associated with a 15% increased risk and a 14% decreased risk of breast cancer, respectively. There was limited evidence on the role of hyperthyroidism treatments in the previous studies. The risk associated with hyperthyroidism was stronger, although not significantly, among postmenopausal women while the breast cancer risk associated with hypothyroidism decreased significantly among premenopausal women. We found no other significant effect modifier.

Comparison to previous or more recent studies

As presented in Chapter I, accumulated evidence in recent years has not provided a clear understanding of the role of thyroid dysfunction on breast cancer risk.

Some (65, 69, 74) but not all studies (46, 47, 64) have suggested that higher blood levels of TSH and thyroid hormone replacement therapy were associated with a reduced risk of breast cancer. Our findings in the UKB showed an inverse association between breast cancer risk and hypothyroidism among women diagnosed before 40 years of age or only after 10 years of hypothyroidism, in partial agreement with previous studies (54, 74, 75).

Two previous nationwide hospital cohort studies and a recent cohort study of female volunteers in clinical trials (74-76) suggested a 1.1-1.2-fold higher breast cancer risk among hyperthyroid women, compared to euthyroid individuals although the association did not reach statistical

significance in the nationwide cohorts (75, 76). In those studies (75, 76), hyperthyroidism was mainly ascertained through hospital databases and one of the cohort studies (75) also had an old population (median age at hyperthyroidism diagnosis: 70 years), which might partly explain the overall elevated risk with hyperthyroidism. In the current study, we did not found a significant association between breast cancer risk and hyperthyroidism overall and (RR=1.08, 95%CI 0.86-1.35), but treated hyperthyroidism (RR=1.38, 95%CI 1.03-1.86). However, information on treatment was either not reported (75, 76) or restricted to ATDs (74) in the three previous studies.

Role of treatments

The estimated cancer risks could have been mediated or modified by thyroid dysfunction treatments. Using data from the UKB, we reported an increased risk of breast cancer that was restricted to treated women (with surgery, RAI, and/or ATDs, no difference in the risks being found according to the treatment modalities). Our meta-analysis suggested that the hyperthyroidism-related increase of risk was the highest among women treated with RAI even though the difference in the risk estimates by treatment subgroups was not statistically significant. There were nevertheless very few studies contributing to the analyses stratified by treatments. Moreover, since the populations may differ in many other aspects than treatments, it is very difficult to disentangle whether those differences reflect the impact of the treatment itself, its impact on thyroid dysfunction, or different severities of thyroid dysfunction and associated comorbidities.

In our cohort study, baseline characteristics did not differ substantially between hyperthyroidism with/without information on treatment (133). The fact that the increase of risk was limited to hyperthyroid women with information on treatments (and that we did not find any increase of risk among those without information) might be explained by the result from the treatments themselves or treatment-related factors. Hyperthyroid patients treated with RAI have been suggested to have a higher breast cancer risk, in relation to the radiation dose received. However, as the possible effect of RAI is modest and observed only after a long latency period (77, 165), it was unlikely the principal cause of the higher breast cancer risk among treated hyperthyroidism in our study. Moreover, we found consistent risks across different modalities of treatment, suggesting that breast cancer risk in treated hyperthyroidism was unlikely attributable solely to a specific treatment modality (e.g., RAI).

Treatments are generally not recommended in subclinical hyperthyroidism when overt conditions are often treated as soon as diagnosed (166). In the current study, hyperthyroid patients without information on treatment could have subclinical hyperthyroidism, which can be endogenous or exogenous (due to over-treated hypothyroidism), while patients with information on treatment might suffer from overt conditions. A recent large population-based linked-record study in the UK found that the majority (74%) of patients with Graves' disease were treated with ATDs (139). Since the recommended length of an ATD course often lasts no longer than 12-18 months, and in the UKB cohort, only ATDs which were regularly being taken at baseline were recorded, and not before, it is possible that hyperthyroid women without information on treatment were treated with ATDs. We found no association with breast cancer risk among these patients in the sensitivity analysis including all those subjects as treated with ATDs. Nevertheless, we always observed higher breast cancer risks among hyperthyroidism treated with definitive treatments (RAI, surgery), which are preferred among patients with recurrent hyperthyroidism (likely having more severe manifestation (167)) or hyperthyroidism caused by toxic nodular goiter. Previous studies have suggested that the higher breast cancer risk associated with hyperthyroidism was strongest among patients with toxic nodular goiters (51, 76). In our study, breast cancer risk did not vary when stratifying by the presence of autoimmune disease. Thus, the etiology of thyroid dysfunction might not be related to the increased risk.

Most (47, 64, 65, 68), but not all (46), previous studies found breast cancer risk increased with increasing blood levels of thyroxine (a marker of hyperthyroidism severity). A recent study which included women without thyroid medication found that increasing blood levels of thyroxine – whatever it was above that reference values or in the euthyroid range – was associated with an increased risk of breast cancer, and thus the risk associated with overt hyperthyroidism was higher than that associated with subclinical conditions (65).

Effect modification by reproductive factors and comorbidities

Few studies have investigated a potential effect modification by menopausal status and other hormonal factors and they found inconsistent results. Some other studies found evidence of a stronger association with high levels of T4 among postmenopausal women compared to premenopausal ones (64, 65), while others showed otherwise (68). In our cohort study, the risk estimates for thyroid dysfunction varied according to menopausal status and late age at

menopause irrespectively of other factors. In the meta-analysis, the insignificant increased risk in the hyperthyroidism analyses could be possibly explained by a limited number of cases, and our findings consistently suggested that the effect of thyroid hormones on breast cancer risk might get stronger among postmenopausal women.

The variation of breast cancer risk related to menopausal status and age at menopause might be related to either genetic predisposition or estrogen levels. Indeed, 40-50% variation in natural age at menopause has also been suggested to be attributable to genetic factors (168, 169). Late age at menopause is a well-documented risk factor of breast cancer, which lengthens the cumulative exposure to cycling reproductive hormones among women (170). After menopause, endogenous estrogen is produced dominantly by the peripheral conversion of androgens in adipose tissue (171), which is represented by BMI. However, in our study, the association between breast cancer and thyroid dysfunction did not vary according to other genetic- and estrogen-related factors. Besides, the proportion of ER+ and ER- breast cancer has been shown to vary according to age at breast cancer diagnosis among both pre- and postmenopausal women (170). In the UKB cohort which does not have detailed information on tumor characteristics, we observed no significant difference in the distribution of age at breast cancer diagnosis according to thyroid dysfunction and menopausal status, suggesting no variation in estrogen-receptor status. Thus, the underlying biological mechanisms of the effect modification by menopausal status and age at menopause remain unclear.

There is limited evidence on the effect modification by reproductive factors other than menopausal status, and comorbidities. Our study was consistent with another nationwide cohort study which showed that the association between thyroid dysfunction and breast cancer risk did not vary according to the presence of obesity or Charlson comorbidity index score (75). Although a recent study showed a positive association between hyperthyroidism and reproductive risk factors of breast cancer (i.e. early age at first birth, breastfeeding for less than a month, and menopausal status) but they did not report breast cancer risk estimates associated with hyperthyroidism according to these characteristics (76). In a large cohort of postmenopausal women, the reduced risk of breast cancer associated with hypothyroidism disappeared among women who used MHT for any duration (74). Among postmenopausal women, the association between T4 and breast cancer risk was also stronger among obese women (68), who had higher estrogen blood concentration than women with normal weight

(171). In the UKB cohort, these findings were not replicated for either overall or treated hyper- and hypothyroidism, although the number of cases in hyperthyroidism analyses was limited

Reverse causation, surveillance bias

The interpretation of our findings as a causal relationship between thyroid dysfunction and breast cancer incidence is still not straightforward.

Indeed, thyroid dysfunction can be subsequent to cancer or cancer treatments. Our UKB study minimized the possibility of reverse causation by excluding prevalent or previous cancer cases at baseline as well as women with less than a year of follow-up. Moreover, the results remained unchanged when we excluded women with less than two or three years of follow-up. The meta-analysis also did not include studies which did not exclude prevalent cancer cases at the time of thyroid dysfunction diagnosis/detection.

Cristofanilli, *et al*. 2005 found that, among women diagnosed with breast cancer, hypothyroid women were more frequently diagnosed with an early-stage or small-size (≤2 cm) tumor than euthyroid women, which suggests that part of the thyroid dysfunction-related excess risks may be associated with non-clinically relevant (over-diagnosed) breast cancers. Women with hyperthyroidism could have more regular health care consultations. However, the increased risk remained after 10 years of hyperthyroidism diagnosis and did not change after accounting for healthcare-related factors (such as adherence to breast/cervical cancer screening recommendations). Accounting for Townsend deprivation score did not change the risk estimates. Thus, a possible surveillance bias was unlikely to be a major explanatory factor.

It is also possible that thyroid dysfunction ascertainment might change along with evolving clinical recommendations for diagnostic thresholds, and assay sensitivity. However, our analyses accounting for calendar year did not show any particular pattern, which suggests that this might not be a factor contributing to a change in breast cancer risk among women with thyroid dysfunction in the UKB cohort.

Summary of current evidence in the literature

Unlike previous meta-analyses (70, 72, 142), we found a significantly increased risk of breast cancer with hyperthyroidism and a significantly decreased risk with hypothyroidism after inclusion of recent large longitudinal studies (65, 74, 133, 151) and exclusion of studies with

prevalent cancers where thyroid dysfunction might result from cancer symptoms or treatment toxicities. Our findings are compatible with two recent large cohort studies reporting an elevated breast cancer risk in relation to increasing T4 and T3 levels within normal ranges (172, 173). High heterogeneity across individual studies was observed for the association between hypothyroidism and breast cancer risk. The degree of heterogeneity was reduced to moderate after the exclusion of the study that showed the most remarkably lower risk of breast cancer associated with hypothyroidism. Thus, the risk estimates varied across studies in terms of the extent of the association, but not the direction. The different ascertainment methods of thyroid dysfunction across studies is probably one factor explaining this heterogeneity since higher risks were estimated in studies based on hospital or health insurance data compared to population-based studies using blood measurements or self-reported data. The different risk estimates between hospital- and population-based studies may also reflect different treatment modalities or severity degrees of thyroid dysfunction or comorbidities. Differences in potential confounding factors, e.g. calendar year, family cancer history, or menopausal status, can also account for some heterogeneity.

Strengths and limitations

Our cohort study has major strengths, including a large population size, a high level of follow-up completeness, and outcome ascertainment through regional cancer and death registries and hospital databases. The crossover among inpatient data and self-reported data on personal medical history allowed us to capture a broad range of health conditions. The UKB also includes detailed information on reproductive factors, lifestyle, socioeconomic status, and family medical history with low proportions of missing data, which allowed us to consider major risk factors of breast cancer. We also were able to conduct an extensive and systematic literature search on the association between both hyper- and hypothyroidism and breast cancer risk, Unlike previous meta-analyses, we applied no restriction on the method for thyroid dysfunction ascertainment to retrieve a maximal number of relevant publications. We excluded studies with cancer history prior to thyroid dysfunction diagnosis/detection to minimize the possibility of reverse causation. Subgroup and sensitivity analyses were conducted to explore potential factors that could explain the heterogeneity of results

However, several limitations can be flagged. Details on cancer stage, grade, and receptor status were unavailable in the UKB, and we could not investigate whether the risk estimates varied

according to tumor characteristics. Lack of information on laboratory measurements of thyroid hormones, etiology, and clinical symptoms of thyroid dysfunction prevented us from determining the severity, the exposure window of thyroid dysfunction (as overt conditions are often treated as soon as diagnosed), and disentangling the independent role of severity, and etiology. Lack of detailed longitudinal information during the follow-up, we were unable to account for thyroid dysfunction diagnosis/treatments for the whole study population during follow-up or to study the independent effects of thyroid dysfunction treatments, and evaluate the impact of different treatment-related factors: RAI dosage, partial versus total thyroidectomy, duration of use and adherence to ATDs prescription. In the hyperthyroidism analyses, given that the higher risks were consistent across different types of treatment, accounting for treatment-related factors would nevertheless be unlikely to change the risk estimates. However, considering the intertwined relationship between hyperthyroidism etiology, severity, and treatment, further research is needed to confirm our findings. The data on comorbidities were also quite limited with no information on the severity, age at onset, and duration of conditions, so it is possible that we did not account for all the possible effects of comorbidities on the association between thyroid dysfunction and breast cancer risk. In the meta-analysis, we found limited evidence in the literature on treatments and important potential confounding factors (e.g. family history of cancer, BMI, reproductive factors) was lacking in most studies, which prevented us from investigating their impact on the pooled risk estimates. High levels of heterogeneity were found across the studies on breast cancer risk after hypothyroidism. This questions the robustness of the pooled risk estimates for hypothyroidism. Last, different measures of association (relative risk, odds ratio, hazard ratio, standardized incidence ratio) were pooled together, which involves the following assumptions: rare outcome (for odds ratio, and hazard ratio), no association between the exposure and censoring status (for hazard ratio) and the use of data from the general population as a comparison group (for standardized incidence ratio) (154, 157), which were nevertheless verified for most studies.

In conclusion, our results suggested that breast cancer risk increased among hyperthyroid women compared to women with no thyroid dysfunction – possibly limited to women with overt / most severe conditions and/or some etiology of hyperthyroidism – while there was a decreased risk among women with hypothyroidism. The association between thyroid dysfunction and breast cancer risk was modified by menopausal status and age at menopause. The increased risk with hyperthyroidism appeared to be limited to postmenopausal women,

while only premenopausal women had a decreased risk with hypothyroidism. Besides, our results suggest that the positive association between increased blood levels of thyroid hormones and breast cancer risk was even stronger with late age at menopause, but did not vary according to other reproductive factors. However, it remains unclear whether these findings represent causal relationships because information on thyroid dysfunction treatments, underlying diseases, cancer stage at diagnosis, and histology was limited in most studies that have been reported so far.

Chapter V Radioactive iodine and breast cancer risk

In the UKB cohort, we found an increased risk of breast cancer associated with treated hyperthyroidism but we were unable to report on the dose-response relationship for RAI – a treatment modality using ionizing radiations which are known to be a carcinogen agent (174) - due to limitations on available data in the cohort. To further study the association between RAI exposure and breast cancer risk, we thus used data from a pooled European cohort of thyroid cancer survivors for which detailed information in RAI activities was collected for a large population of women treated at a similar age range as hyperthyroid women. Though different dose levels are typically used for the treatment of hyperthyroidism (~10-20 mCi) and treatment of thyroid cancer (~100-≤200 mCi), we hypothesized that the dose-response curve estimated among thyroid cancer survivors can be extrapolated to hyperthyroid women.

V.1 Methods

V.1.1 Study population

Among female thyroid cancer survivors in the European pooled cohort (Chapter II.2), we excluded patients with external radiotherapy prior to thyroid cancer diagnosis (n=80), any malignancy in the two years after thyroid cancer diagnosis (n=273), less than two years of follow-up (n=543), or those who were diagnosed at the age of 95 or more (n=1). Finally, our study population included 8,475 women (Figure 18).

Follow-up time started on the date of thyroid cancer diagnosis and ended on the date of any second cancer diagnosis (except non-melanoma skin cancer), death, the last visit to the treatment center, or the end of the study period (31 December 2004, 31 December 2008, and 31 December 2014 for the Swedish, Italian, and French cohorts, respectively), whichever occurred first. We censored the follow-up at age 95 years because beyond that age, cancer records are likely to be inaccurate (n=31), and at the start date of external radiotherapy, if any, in the Italian cohort because of the unavailability of technical parameters needed for the dose calculation (n=14).

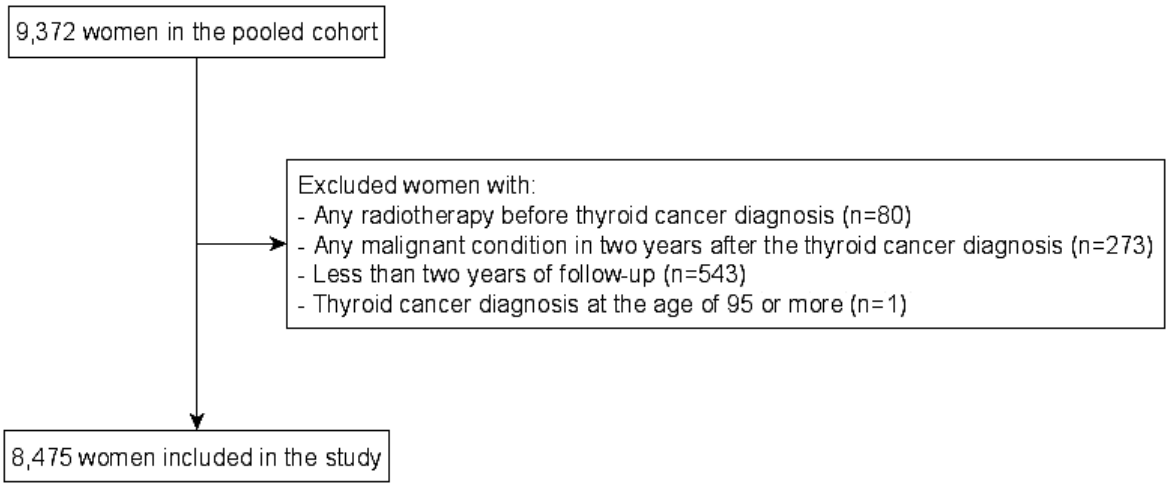


Figure 18 Flowchart of the study which used data from the European pooled cohort

We retrieved information on thyroid cancer diagnosis, treatment modalities (surgery, external radiotherapy, and internal radiotherapy with RAI), internal and external radiotherapy administration date, and their administered activities from medical records of each cancer center. Invasive subsequent cancer cases and deaths were ascertained with medical records in the French and Italian cohorts, and retrieved in the national cancer and death registries in the Swedish cohort.

V.1.2 Statistical analyses

Model building

We used Poisson regression models (Chapter III.3) to investigate the breast cancer incidence associated with RAI treatment among our study populations. Details information on model building are presented in Appendix 6. The use of RAI treatment (yes/no) and cumulative activity (no RAI treatment/ <40/ 40-100/ 100-200/ 200-400/ ≥400 mCi) were analyzed as time-dependent variables. We supposed ten years as the shortest time needed for the development and detection of breast cancer after RAI treatment or external radiotherapy (hereafter, minimal latency time), in agreement with previous studies (175-177). Accordingly, the relative risk (RR) of subsequent breast cancer at a given calendar period and attained age was modeled as a function of the expected number of breast cancer from the reference rates, and of the cumulative activity of RAI treatment administered ten years or more before. We further adjusted for country, age at thyroid cancer diagnosis, and cumulative dose of external radiotherapy except

where stated otherwise.

The absolute excess risk (AER) was calculated as the observed minus expected number of neoplasms, divided by the person-years at risk and multiplied by 10,000. We also estimated excess relative risks (ERRs) per 10 mCi (0.37 GBq), and evaluated possible departures from linearity for the shape of dose-response models for therapeutic RAI cumulative activity by comparing models with linear terms, linear-quadratic terms, and linear-exponential terms (Appendix 6). We evaluated possible linear threshold models which specify a linear relationship starting at a threshold activity (i.e., an activity below which there is no radiation effect). The likelihood function was calculated over a wide range of possible threshold values, and the one with the highest likelihood was used as the estimate of the threshold (Appendix 6) (178).

Assessment of modifying effects

Possible effect modifications by external radiotherapy, age/year at diagnosis, and follow-up time were evaluated by testing the statistical significance of an interaction term between RAI treatment and the studied covariate (likelihood-ratio χ^2 tests).

Sensitivity analyses

Several sensitivity analyses were conducted.

(1) We computed risk estimates incorporating both RAI activities for diagnostic and therapeutic purposes.

(2) As the external radiation dose was imputed in a considerable proportion of women treated with external radiotherapy (48.1%), we censored women after 10 years of external radiotherapy.

(3) We also set 31 December 2003 and 31 December 2009 as the endpoint of the study for the Italian and French cohorts, respectively, since without a recurrence, medical surveillance is more likely to be less frequent after five years of diagnosis.

(4) We also evaluated the association between breast cancer risk and RAI estimated cumulative absorbed doses among women aged >15 years at thyroid cancer diagnosis.

(5) Because RAI-treated women could be different from women without RAI treatment in

terms of indications and lost of follow-up, we conducted several analyses to further understand to which extent this could bias the risk estimates: First, we considered lost of follow-up as our primary outcome (instead of breast cancer diagnoses) in a sensitivity analysis. Second, we applied inverse probability weighting (IPW) accounting for the probability of receiving RAI treatment, external radiotherapy and of lost of follow-up (Appendix 6).

Analyses were performed using SAS software (SAS Inc., Cary, NC) and the EPICURE AMFIT statistical software package. 95%CIs were estimated with maximum likelihood methods. When lower bounds could not be estimated, results from Wald estimation were calculated.

V.2 Results

V.2.1 Population description

In the pooled cohort of 8,475 women treated for thyroid cancer, 5,292 (62%) were treated with RAI treatment and 970 (11.4%) with external radiotherapy (Table 16). RAI-treated patients received a median cumulative activity of 100 mCi (range 10-1,597 mCi) – equivalent to 3.7 GBq. The median cumulative doses to the breasts from RAI therapy and external radiotherapy were 247 mGy (range 25-3,942 mGy), and 566 mGy (range 1-46,595 mGy), respectively (Table 16). Compared to women without RAI treatment, RAI-treated women were more likely to be lost of follow-up, and to receive diagnostic RAI, but not external radiotherapy (Supplementary table 6, Supplementary table 7).

V.2.2 Dose-response relationship between RAI and breast cancer risk

During a median follow-up of 12.7 years, 335 women developed a breast cancer. We found no evidence of departure from linearity in the shape of dose-response models for RAI activities. Overall, we found no significant association between RAI therapy and subsequent breast cancer risk (RR=1.07, 95%CI 0.84-1.35, AER per 10,000 person-years=0.8, 95%CI: -4.9-6.4). However, there was a significantly increased risk with increasing RAI activity (ERR per 10 mCi = 1.7%, 95%CI: 0.2 to 3.8%), corresponding to an ERR per 10 mGy of 0.5% (95%CI: 0 to 1.4%). Exposure to an RAI cumulative activity of 10 mCi could induce only 0.41 excess cases of breast cancer for every 10,000 person-years of follow-up. The highest risk was among women who received a cumulative RAI activity of ≥400 mCi (RR=2.41, 95%CI 1.13-3.52,

AER per 10,000 person-years=42, 95%CI: -8 to 93) (Table 17). Examining deviances to estimate the threshold dose, we found the minimum deviance of the linear threshold models at 80 mCi with the upper limit of the 95%CI at 184 mCi (Figure 19).

We found neither significant modifying effects of other factors (Supplementary table 8), nor substantial difference between the main analyses and the sensitivity analyses. Analysis accounting for IPW even showed a stronger effect of RAI treatment (Supplementary table 9).

Table 16 Characteristics of the pooled cohort

	France (N=5,469)	**Italia**[1] (N=1,551)	**Sweden** (N=1,455)	**Pooled cohort** (N=8,475)
Year of treatment, year, median (min-max)	1993 (1934-2005)	1988 (1958-1996)	1965 (1950-1983)	1989 (1934-2005)
Age at thyroid cancer diagnosis, year, mean (min-max)	44 (2-90)	44 (5-81)	49 (5-90)	44.5 (2-90)
Follow-up time, year, median (min-max)	12 (2-66.5)	11 (2-37)	24 (2-55)	12.7 (2.0-66.5)
Breast cancer cases, n (%)	202 (3.7)	38 (2.5)	95 (6.5)	335 (4.0)
Time to breast cancer, year, median (min-max)	12 (2-55)	12 (2-35)	25 (2-46)	14.1 (2.0-55.2)
Treatment of thyroid cancer by ionizing radiation				
External radiotherapy, n (%)	430 (8)	-	540 (37)	970 (11.4)
Therapeutic RAI activity, n (%)	3,403 (62)	1,307 (84)	582 (40)	5,292 (62)
- Number of therapeutic RAI activity, median (min-max)	1 (1-14)	1 (1-15)	1 (1-10)	1 (1-15)
- Cumulative activity of therapeutic RAI, mCi, median (min-max)	100 (10-1,597)	100 (25-1,491)	75 (10-1,330)	100 (10-1,597)
Cumulative radiation dose delivered to the breasts				
Therapeutic RAI activity, mGy, median (min-max)[2]	247 (25-3,942)	247 (61-3,680)	185 (25-3,283)	247 (25-3,942)
External radiotherapy, mGy, median (min-max)	1,299 (10-43,480)	-	272 (1-46,595)	566 (1-46,595)
- Imputed dosimetry for external radiotherapy, n (%)	61 (14)	0	406 (75)	467 (48)

[1] Patients with external radiotherapy were excluded at inclusion or censored at the start date of external radiotherapy

[2] Patients aged >15 years at thyroid cancer diagnosis

Table 17 Breast cancer risk associated with therapeutic RAI (considering a ten-year latency time)

		Pooled cohort	
	BC cases	**RR[1] (95%CI)**	**AER[2]**
Therapeutic RAI activity			
No	234/85,715	1	
Yes	101/27,685	1.07 (0.84-1.35)	
P-heterogeneity		*>0.5*	
Cumulative activity of therapeutic RAI (mCi)			
No RAI	234/85,715	1	
<40	4/2,316	0.49 (0.15-1.15)	
40-100	16/6,499	0.77 (0.44-1.25)	
100-200	53/14,029	1.10 (0.80-1.47)	
200-400	19/3,731	1.55 (0.92-2.44)	
≥400	9/1112	2.41 (1.13-4.52)	42 (-8-93)[3]
P-heterogeneity		*0.039*	
P-trend		*0.028*	
ERR per 10 mCi[1]	0.017 (0.002-0.038)		

AER: Absolute excess risk per 10,000 person-years, BC: Breast cancer, CI: Confidence interval, ERR: Excess relative risk, RAI: Radioactive iodine, RR: Relative risk

[1] Adjusted for country, age at diagnosis, and dose of external radiotherapy delivered to the breast in the background risks

[2] AER are shown only when the corresponding RRs were statistically significant at P<0.05

[3] Wald's estimation

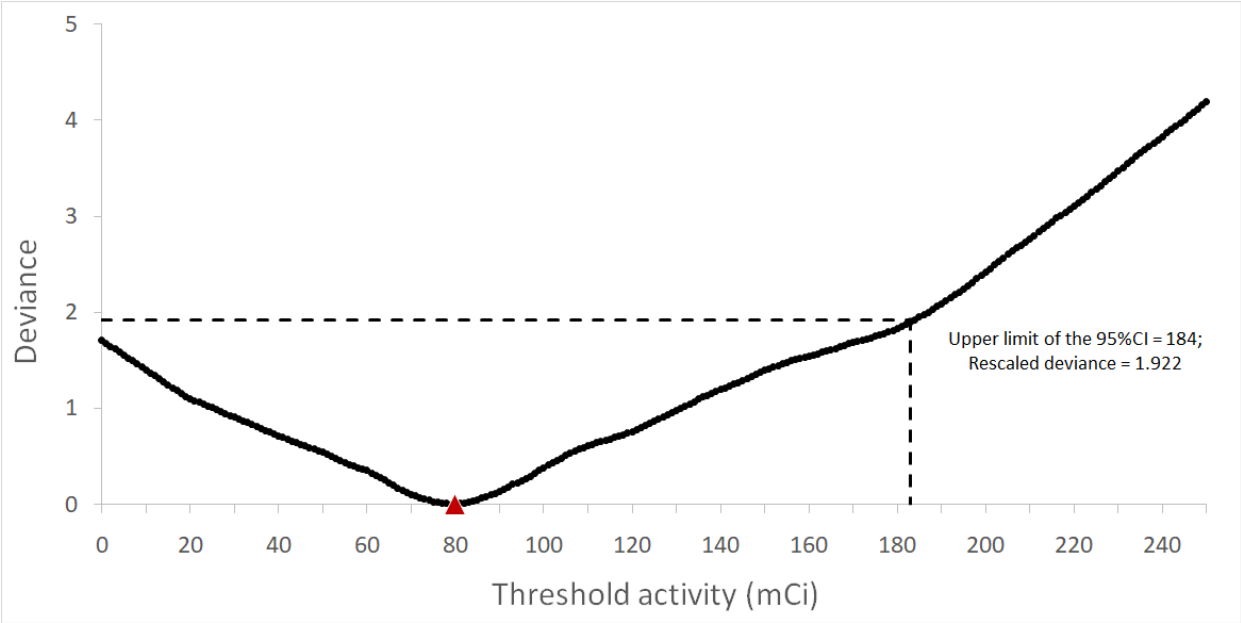


Figure 19 Deviances for linear ERR models given a threshold dose (0-250 mCi)

Deviances rescaled to zero at the minimum deviance (triangle symbol). Dash line identifies the upper limit of the 95% confidence interval

V.3 Discussion

In the current study, we found a linear dose–response relationship between cumulative RAI activities and breast cancer risk after a minimal latency time of 10 years. The estimated ERR was 1.7% per 10 mCi (which was equivalent to 0.5% per 10 mGy). It translated into 0.4 excess cases of breast cancer per 10,000 person-years receiving a RAI exposure of 10 mCi – the typical activity used for treatment of hyperthyroidism. Estimate of a threshold activity was 80 mCi with an upper 95% confidence bound of <200 mCi.

Relative and absolute risks of breast cancer incidence related to RAI exposure

Exposure to ionizing radiation has been demonstrated to increase the lifetime risk of breast cancer among women (175). However, the ionizing radiation-related estimated risks varied considerably across medically, occupationally, environmentally exposed populations in the previous studies. Our increased risk of 0.5% per 10 mGy of RAI absorbed dose to the breasts was 2-4 fold higher than the risk associated with external radiation therapy among cancer survivors (ERR/100 mGy varied from 0.01 to 0.03) (179), but of the same magnitude than the risk estimates reported from the US Radiologic Technologists Study (ERR/100 mGy=0.07, 95%CI: -0.01-0.19) (180), the Life Span Study of Atomic Bomb Survivors (ERR/100 mGy varied from 0.09 to 0.11) (181, 182), and the Techa River Incidence Cohort (ERR/100 mGy: 0.19, 95%CI: -0.06-0.61) (183) (Appendix 8: Supplementary table 10). These discrepancies could possibly due to differences in radiation sources (e.g. dose rate), dose ranges, age at exposure, and background risks. Hypotheses and approximations used for the dose reconstruction might also contribute to the differences. Whereas the absorbed dose from RAI depends on the distance between the source organs and the target reference dose coefficients, i.e., S-values, was used to compute breast doses without accounting for the specific anatomy of each patient, which was lacking from the available treatment records. In a recent study which was the first one providing direct evidence of an association between internal exposure from RAI and breast cancer risk, Kitahara et al. found an increase of breast cancer mortality of 10% per 370 MBq (10 mCi) (55), which was compatible with our estimate.

Providing that the hypothesis of linearity in the dose-response relationship for exposures ranging from ~10 to 500 mCi is true, breast cancer risk is likely to be very small for the range of RAI activities typically used for treatment of hyperthyroidism (10-15 mCi for Graves'

disease, 10-20 mCi for toxic nodular goiter) (31), and we did not show any statistically significant increase of risk for activities <100 mCi, but for activities >=200 mCi. A few previous studies reported no increased risks related to RAI cumulative activities of >4.4 GBq or 150 mCi after adjusting for important confounders, but the follow-up time was probably too short (median follow-up time: 6-7 years) given the long latency time between radiation exposure and radiation-related breast cancer incidence (184-186). According to previous studies on external radiation exposure, the minimal latency time is likely to be around 10-15 years (175, 177). This is in agreement with our results of an ad hoc analysis: considering a 5-year minimal latency time, we found a lower goodness-of-fit of the dose-response model (ERR = 1.2%, 95%CI -0.1% to 2.9%, p-trend=0.10, AIC=3,749) than when considering a 10-year minimal latency time (AIC=3,607).

Effect modifications

In our study, we found no evidence of an effect modification by the exposure to external radiotherapy, age/year at thyroid cancer diagnosis, and follow-up time. Our null results on the role of age at thyroid cancer diagnosis is apparently in contradiction with previous studies which reported highest risks among women exposed before the age of 30 (175, 182), especially around menarche (182). However, in our study, there was a large proportion of patients diagnosed at the age of adulthood (80% of patients aged ≥30 years at thyroid cancer diagnosis), which prevented us to observe such effect modifications for early age categories.

Indication bias, selection bias due to lost of follow-up, and surveillance bias

Although the increased risk of breast cancer among women with a high cumulative activity of RAI is biologically plausible and in line with numerous epidemiological studies on (external) radiation exposure, our results could also be due – at least in part - to indication bias, selection bias due to lost of follow-up, and surveillance bias. Thyroid cancer survivors who received a high cumulative activity of RAI could have worse prognostic factors and a higher probability of cancer recurrence (187, 188), which require further management, possibly leading to a better follow-up and a more intensive screening strategy than women without RAI treatment or with lower cumulative activity. However, to date, no specific breast cancer screening program has been recommended for thyroid cancer survivors. Analyses considering a long latency time of 10 years after the exposure of RAI also minimized the impact of a potential surveillance bias.

Restricting analyses to the Swedish population which has a complete, passive (non-selected) follow-up for all individuals through the national registries did not substantially change the risk estimates. Surprisingly, the results from sensitivity analyses which had considered lost of follow-up as an outcome or used inverse probability weighting (that aimed to neutralize the differences caused by a possible indication and/or selection bias) suggested that the risk could have been underestimated among women with the highest cumulative activities of RAI (Appendix 8).

Strengths and limitations

The current study has major strengths, including a large population size from three major cohorts, with a confirmed thyroid cancer diagnosis and long follow-up periods, which is crucial since the possible effects of RAI are considered to be modest and can be subject to long latency times. The pooled cohort also includes detailed information on administration dates and activities for RAI treatment and external radiotherapy. To investigate breast cancer risk associated with RAI treatment, we were able to use both administered activities and the estimate of absorbed doses, which enabled us to yield risk estimates more precisely and compare results with previous studies. In addition to an external comparison group with the general population, we also had an internal comparison group of thyroid cancer patients who did not receive RAI treatment, which helped s to minimize indication bias.

We acknowledge several limitations. The study population was not women with hyperthyroidism, but thyroid cancer survivors. Details on cancer stage, grade, as well as breast cancer form (unilateral or bilateral), and receptor status were unavailable. Lack of information on relevant confounders such as obesity, hormonal factors requires caution when interpreting the results. Besides, some genetic characteristics/disorders such as Cowden syndrome are common causes of both thyroid and breast cancer and we were not able to account for those factors in the current study. We were not able to estimate reliable absorbed doses from RAI administrations for women aged 15 years or less at thyroid cancer diagnosis, and the risk estimates related to RAI absorbed dose might not be transposable to this population. Finally, we could not obtain information on diagnostic RAI administrations or estimate doses to the external radiotherapy for the whole population.

In conclusion, we found that RAI treatment is associated with a long-term increase in breast

cancer risk. However, the excess risk possibly induced by RAI within the typical dose range used for hyperthyroidism is likely to be very small (EAR per 10 mCi=0.41 cases per 10,000 person-years). Further investigation is needed to confirm the risks related to exposure of RAI among hyperthyroid patients and to investigate the interaction with potential effect modifiers.

Chapter VI General discussion

This chapter summarizes the main findings of the thesis, and provides our interpretation of the results, their potential implications for clinical care, and our proposal for future research.

VI.1 Main findings

Although thyroid dysfunction is common among adult women, it cannot be completely cured in most cases, but controlled with regular monitoring and appropriate treatments. This raises concerns about the long-term outcomes in individuals suffering from these conditions, from both the treatments and the conditions *per se*. This thesis project was conducted in the context of the unfinished story about potential associations between thyroid dysfunction and cancer risk, despite evidence that has been accumulated over the recent decades. In this thesis, we investigated a possible association between thyroid dysfunction and female breast cancer risk – given that both conditions are strongly associated with female reproductive hormones – and we examined the potential role of thyroid dysfunction treatments, comorbidities, and other breast cancer risk factors on this association. The research was mainly based on data from 239,436 women who were aged 40-69 years at their enrollment in the population-based UKB cohort in 2006-2010, which we combined in a meta-analysis with all current evidence in the literature that we identified through a comprehensive systematic review of observational studies. In addition, we investigated the role of RAI treatment (which can be used to treat hyperthyroidism) on female breast cancer risk, using data from 8,475 women who were treated for thyroid cancer in 1934-2005 and included in a pooled analysis of three European cohorts.

The population-based study and the meta-analysis (chapter IV) showed that compared to euthyroidism, hyper- and hypothyroidism were associated with significantly higher and lower risks of breast cancer, respectively. In the UKB cohort, with a median follow-up time of 7.1 years, the higher risk of breast cancer among women treated for hyperthyroidism could be explained by hyperthyroidism severity, and/or etiologies whereas we found no difference in risk estimates among treatment modalities (ATDs, RAI, and surgery). We found similar results in the meta-analysis ($p_{\text{heterogeneity among treatments}}$=0.44), although the meta-analysis did suggest a higher relative risk in populations treated with RAI (RR=1.54, 95%CI 1.08-2.19) than in populations with unreported treatments (RR=1.13, 95%CI 1.04-1.22). In chapter V, we

demonstrated that breast cancer risk increased in a dose-response manner with increasing doses of RAI treatment (ERR=1.7% per 10 mCi) after a long latency time (minimum of 10 years). However, no significantly increased risk was found at typical activities of RAI for hyperthyroidism (10-20 mCi). Thus, our results suggested that the increased risk of breast cancer among hyperthyroid women was mostly associated with higher thyroid hormone levels, and not treatments *per se*. Our studies also suggested the effect of increasing thyroid hormone levels might be strengthened among postmenopausal women, especially those who experienced late menopause (Chapter IV). In this thesis project, we did not find any evidence that comorbidities, other reproductive factors or surveillance bias modified the associations between thyroid dysfunction and the incidence of breast cancer.

VI.2 Interpretation

VI.2.1 How thyroid dysfunction can be associated with breast cancer risk: a story of hormone levels?

As presented in chapter I, several explanations for the role of thyroid hormones on breast cancer development have been explored *in vitro* and *in vivo*. T4 and T3 activate MPAK pathways and phosphorylate ERα, inducing cell proliferation (60, 189, 190). T3 can also enhance the effect of estrogens on breast cell proliferation (191), and directly increases aerobic glycolysis, a hallmark of cancer, which is known as the Warburg effect (60). T4 is known to have anti-apoptotic properties, which act via the integrin αvβ3, by stimulating gene expression of cancer cell defense (4, 62). Moreover, excessive or insufficient iodine intake, which plays a key role in thyroid hormone production, could also be a risk factor for breast cancer (63). Taken together, current experimental evidence supports a positive association between high levels of thyroid hormones and a higher risk of breast cancer.

By assuming that higher thyroid hormone levels are associated with an increased breast cancer risk, it is possible that breast cancer risk varies according to thyroid dysfunction-related factors, such as the duration of exposure, and whether breast cancer risk is associated with changes in thyroid hormone levels when the thyroid condition is controlled. In the UKB cohort, we found an increase of risk among women who were diagnosed with treated hyperthyroidism for 5-10 years, although the number of cases was limited. There was a lower risk among women diagnosed with hypothyroidism for more than 10 years. However, because information on

thyroid dysfunction status was only available for the whole population at baseline, and not afterward, thyroid dysfunction status might change during the follow-up, possibly leading to a change in breast cancer risk. This lack of longitudinal information on thyroid dysfunction also exists in all previous studies in the literature.

VI.2.2 Is the higher breast cancer risk among hyperthyroid women caused by hyperthyroidism treatments?

In Chapter IV, we reported a 38% increased risk of breast cancer among women with treated hyperthyroidism. Of possible explanations, previous studies have suggested hyperthyroidism treatments (165) or etiologies (51, 76), which, in this context, could refer to toxic multinodular goiter or recurrence of Graves' disease. The risk associated with treated hyperthyroidism did not vary according to the treatment type (ATDs, RAI, or surgery). In the meta-analysis, stratified analyses by treatment modalities for hyperthyroidism showed no statistically significant difference across populations treated with different treatment modalities, although the results arose from limited data. This result needs to be carefully interpreted since (1) previous studies did not have the necessary information on hyperthyroidism treatments, and the focus was only on RAI in a small number of studies; (2) the management of hyperthyroidism differs according to age and country and the data were too limited to account for the three factors simultaneously; (3) RAI and surgery for hyperthyroidism often result in hypothyroidism, which may complicate the interpretation of studies, especially the most recent ones where definitive treatments of hyperthyroidism (i.e. RAI or surgery) are more frequently used including as first-line treatments, and thus lead more frequently to subsequent hypothyroidism. However, in the UKB cohort, the association remained whether hyperthyroid individuals subsequently developed hypothyroidism or not, suppressing concerns over confounded risk estimates due to iatrogenic hypothyroidism. Our findings are in favor of an increased breast cancer risk related to severe cases of hyperthyroidism, which is supported by other studies reporting risk estimates varying with blood levels of thyroid hormones (64-66). Our results thus support the assumption that higher thyroid hormone levels could play a key role in the development of female breast cancer, but do not eliminate a potential role of treatments, especially RAI.

Therefore, we investigated the specific role of RAI on breast cancer risk in Chapter V. Among 8,475 women followed during a median follow-up time of 12.7 years after a diagnosis of

differentiated thyroid cancer, we found that increasing cumulative RAI activity was associated with an increased risk of breast cancer, with no evidence of a departure from linearity in the dose-response relationship (ERR = 1.7% per 10 mCi, 95%CI=0.2-3.8%). However, this result was driven by high exposures (200- >400 mCi), with no statistically significant increase found for cumulative exposures <200 mCi. From the estimated risk per mCi, we projected that exposure to 10-mCi RAI activity could induce 0.41 excess cases of breast cancer for every 10,000 person-years.

RAI is a simple, reliable, and cost-effective option for treating hyperthyroidism, but its benefit-harm balance has been questioned. Although the choice of treatment modality for Graves' disease varies according to countries, there has been a shift in recent years in treatment preferences towards RAI rather than surgery in the UK. According to the recent NICE recommendations for the management of hyperthyroidism, RAI should be offered as the first-line definitive treatment for most people with hyperthyroidism secondary to Graves' disease (35). For adults who are likely to have a particularly good response to ATDs (mild uncomplicated Graves' disease), RAI and a course of ATDs could be equally appropriate options. Indeed, accumulating evidence has shown that RAI treatment provides better long-term outcomes than ATDs in controlling thyroid hormone levels, although at a higher risk for exacerbating Graves' orbitopathy while there was no convincing evidence of a difference between RAI and surgery. Although radiation exposure could lead to a small increase in cancer risk, our findings demonstrate that RAI is unlikely a major factor explaining the higher breast cancer risk reported in this thesis and in the literature among hyperthyroid women. The absolute excess cancer risk related to radiation exposure would be very small and certainly outweighed by the expected benefits of this treatment modality of hyperthyroidism.

VI.2.3 Are there any other factors that could modify and/or explain the association between thyroid dysfunction and breast cancer risk?

VI.2.3.1 Reproductive factors, comorbidities, and other confounding and modifying factors

We observed significant changes in thyroid dysfunction-related breast cancer risk by menopausal status and menopausal age. Our findings suggest that the increased risk of breast cancer associated with higher thyroid hormone levels was more pronounced among postmenopausal women, especially among those who experienced late menopause. The reasons

explaining the stronger association of thyroid hormone levels and breast cancer risk in postmenopausal women are unclear. There could be a close link between thyroid hormones and estrogens, and it has been suggested that thyroid hormones could contribute to breast cancer development in estrogen-similar pathways. It can also be hypothesized that the reduced risk associated with low blood levels of thyroid hormones cannot counteract the stronger effect of estrogens in women with late menopause. Further studies investigating the interaction between thyroid hormone and estrogen levels are needed to confirm our findings.

Apart from menopausal status, little evidence exists in the literature regarding the role of potential confounding or modifying factors on the association between thyroid dysfunction and breast cancer risk and we could not conduct an analysis accounting for these factors in our meta-analysis. Our findings of no modifying effects of comorbidities in the UKB cohort were consistent with a nationwide study that showed unchanged breast cancer risk associated with thyroid dysfunction according to BMI and scores of Charlson comorbidity index (75). Recent studies reported inconsistent results of the potential role of BMI and menopausal hormone therapy (MHT), which both had a close link to estrogen levels in postmenopausal women (65, 68, 74) as adipose tissue is the main source of estrogen biosynthesis and exogenous estrogen sources and MHT is an established risk factor of breast cancer. In the UKB cohort, we did not find any significant modifying and confounding effects of these factors, as well as other reproductive factors, lifestyle, socioeconomic status, or family medical history. However, in the hyperthyroidism analyses, the limited number of cases in our study compared to other recent studies (68, 74) might be a possible explanation for the null association.

VI.2.3.2 Other factors

Women at risk for hyperthyroidism may also be at risk for breast cancer. Hyperthyroidism was associated with breast cancer risk factors such as mammographic density (toxic nodular goiters only), age at first birth, and duration of breastfeeding (76). In the thesis project, the association remained even after adjustment for age at first birth, and duration of breastfeeding, which suggests that the significant change in breast cancer risk among women with thyroid dysfunction in our study cannot be explained by these confounding factors.

Another hypothesis is that hyperthyroid women would see their doctors more often, especially during the first years after the diagnosis, and therefore are more likely to get screened for other

problems such as breast cancer. By excluding the first year of follow-up in the principal analyses, we minimized such a potential surveillance bias in the study of the UKB cohort. The results also did not change when we excluded up to three years of follow-up. In the meta-analysis, the higher pooled risk ratio of breast cancer incidence among hyperthyroid women did not change when including only studies with available risk estimates after at least one year of follow-up. Moreover, currently, no specific breast cancer screening program has been recommended for women with thyroid dysfunction. In sensitivity analyses, we accounted for women's adherence level to the national recommendations for breast cancer screening, and adherence to recommendations for breast cancer screening was not a significant confounding or modifying effect in our study. Our findings demonstrate it is unlikely that surveillance bias could be the main contributing factor in the association between thyroid dysfunction and breast cancer risk. However, we were unable to rule out completely the possible over-diagnosis due to the lack of information on breast cancer stage and grade.

VI.3 Clinical implications

In the context where there are conflicting results on the association between thyroid dysfunction and breast cancer risk, the findings from this thesis project provide clear evidence of a higher risk related to increased thyroid hormone levels above normal ranges. Our project thus lends support for the hypothesis of the potential roles of thyroid hormones in breast cancer development and highlights the need of urging women with hyperthyroidism, especially after menopause, to become vigilant of the increased risk of breast cancer and have regular follow up for breast cancer screening. Moreover, although the thesis suggests that the excess risk of breast cancer related to RAI treatment for hyperthyroidism is very small, since cancer risk related to radiation exposure might increase in a dose-response manner, both clinicians and patients should still be aware of the potential risks. To be on the side of caution, people who have undergone RAI treatment should be treated with a dose that is as low as reasonably achievable.

VI.4 Perspectives for future research

The association between breast cancer and thyroid dysfunction remains unclear, which reflects a mixture of circumstances. Both thyroid dysfunction and breast cancer are heterogeneous conditions with various etiologies and risk factors. The definition of thyroid dysfunction (e.g.

reference ranges of TSH and thyroid hormone levels), and its clinical management vary across geographic regions. Second, growing knowledge of the complex biology of breast cancer suggests a need to reframe hypotheses by focusing more on examining associations with tumors of specific types and considering mechanistically driven gene–disease-environment interactions. Third, for a wide array of relating factors and their (potentially) complicated associations, conventional methods might not be optimal to elucidate the association between thyroid dysfunction and breast cancer risk. Draw on the insights developed in this thesis, we suggest recommendations for future research:

VI.4.1 Study design

Research needs include more detailed and better quality data on thyroid dysfunction ascertainment, ideally making use of both repeated measurements of thyroid hormones over time and clinical validation. Important examples include detailed data on thyroid dysfunction etiologies, thyroid hormone levels on the date of diagnosis and during the follow-up assessment. Comprehensive details on treatment modalities after thyroid dysfunction diagnosis such as the types of treatment, the date of initiation, the duration and dosage (for ATDs, and thyroid hormone replacement therapy), and administered (for RAI) would also be required. If thyroid dysfunction status and (un)controlled conditions after the diagnosis is not available, better indicators could be developed through treatment ascertainments, for example, initiation of THRT after an RAI session, without the use of ATDs.

Equally important are large-scale prospective settings with a complete, passive follow-up and detailed data on breast cancer tumor pathology such as TNM stage at diagnosis, grade, estrogen receptor, progesterone receptor, and HER-2 status.

VI.4.2 Statistical analyses

Once necessary data have been collected, stratified analyses on tumor characteristics are needed to (1) address the surveillance bias dilemma, and (2) to study whether thyroid hormones promote specific breast cancer subtypes. Moreover, stratification by receptor status of breast tumor would be beneficial to explore the intertwined relationship of thyroid hormones and sex hormones, such as estrogen, along with stratification analyses by menopausal status and/or age at menopause.

Analyses on thyroid dysfunction-related characteristics in risk assessment would allow determining high-risk populations and time-depending analyses that account for the change of either thyroid dysfunction or treatment status would be necessary. In such research, because of the time-depending confounding/mediating factors such as treatments, a causal framework could be employed to investigate the different associations between thyroid dysfunction, treatments, comorbidities/complications, and breast cancer.

VI.4.3 Causal framework: A proposal for future research

As presented in chapter IV, it is complicated to disentangle the intertwined association between hyperthyroidism etiologies, severity, and treatments, and breast cancer risk as these factors have mutual interactions over time. To date, all previous studies used women without thyroid dysfunction as the internal comparison group and the risk estimates are valid only when assuming that thyroid dysfunction status and treatments are time-fixed variables, which is not always a proper approach. It might also be beneficial to decompose the effect of hyperthyroidism according to etiologies, and that of treatments on breast cancer risk among hyperthyroid women. Accordingly, this type of study comparing different treatment options for hyperthyroidism may help to better inform clinical treatment practices and guidelines. In this section, we propose a causal framework (Chapter III.4), which could apply to observational studies, to investigate the direct and indirect effects of hyperthyroidism, and treatments on the risk of breast cancer.

Researchers could perform the causal mediation analysis following four steps: (1) Formulate a causal DAG, (2) fit multivariate models to the data following the DAG, (3) choose mediation definitions and corresponding intervention scenarios, and (4) use the established multivariate models in the G-formula to simulate these scenarios.

VI.4.3.1 Directed acyclic graph

We assume that our exposure of interest, Graves' disease, and toxic nodular goiter, causally influences treatments, and breast cancer incidence (Figure 20). Hyperthyroidism (Graves' disease, toxic nodular goiter) influences breast cancer incidence directly and indirectly through potential mediators including hyperthyroidism treatments, uncontrolled hyperthyroidism, and iatrogenic hypothyroidism. RAI and surgery are supposed to lead to iatrogenic hypothyroidism

whereas ATDs could result in a state of uncontrolled hyperthyroidism, which in turn has causal impact on the subsequent receipt of RAI or surgery. Uncontrolled hyperthyroidism, iatrogenic hypothyroidism, and hyperthyroidism treatments are considered as time-depending mediators. The omission of variables and arrows represents our causal assumptions, e.g. we assume that surgery does not cause a change in breast cancer risk. The solid lines between variables describe hypothesis-driven association and the dash line between the use of ATDs and breast cancer incidence indicates a possible, but not hypothesis-driven, association.

Confounders vary across pairs of variables, and are not shown in the DAGs to facilitate its reading. If using data from the UKB cohort, we would consider attained age as a confounder for all pairs of variables while age at menopause, age at menarche, parity and age at first childbirth, oral contraception, MHT, alcohol consumption, smoking, physical activity, personal history of benign breast disease, mammography, cervical smear test, Townsend score as confounders for the association between Graves' disease/Toxic nodular goiter and breast cancer incidence.

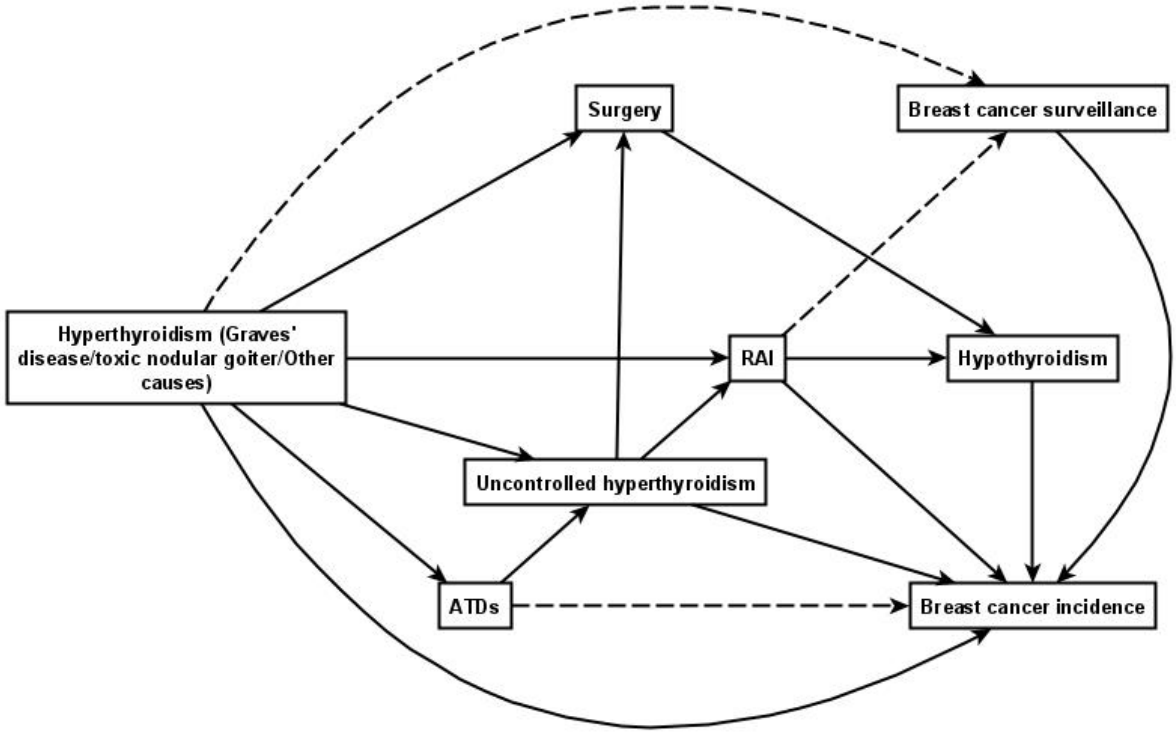


Figure 20 Proposed directed Acyclic Graph

VI.4.3.2 Multivariate models

After formulating the causal DAG, researchers need to generate prediction multivariate regression models for hyperthyroidism, uncontrolled hyperthyroidism, iatrogenic hypothyroidism, ATDs, RAI, surgery, and breast cancer incidence as a function of their relevant set of covariates. Ideally, the status of the abovementioned time-dependent variables in year N+1 is calculated based on data of the times 0 through N. Because the model building might become overelaborate in case of a long time of follow-up, researchers could limit assumptions on causality within a hypothesis-driven certain amount of time. Categorical variables (e.g. uncontrolled hyperthyroidism) could be modeled with (multinomial) logistic regressions and continuous variables (e.g. cumulative RAI activities) with generalized linear regression models.

VI.4.3.3 Mediation definitions and corresponding intervention scenarios

Mediation definitions and corresponding intervention scenarios should be determined depending on the research questions. However, it is often necessary to reframe the research questions from a causal perspective. For illustration, we present two examples of research question, their corresponding causal interpretation, and technical terms in the models concerning related variables and scenarios.

Research question: Is toxic nodular goiter, but not Graves' disease, the cause of the higher risk of breast cancer among hyperthyroid women?

> *Question in the causal analysis: What would have happened to breast cancer risk if all individuals in our study population had had Graves' disease versus what would have happened if all individuals in our study population had had toxic nodular goiter?*
>
> *In the prediction models, the input variables would be set to values outlined in the scenarios 1 and 2 in Table 18.*

Research question: Among women with Graves' disease, does being treated with RAI increase breast cancer incidence?

> *Question in the causal analysis: What would have happened to breast cancer risk if all individuals in our study population had had Graves' disease and the initial treatment had been*

RAI versus what would have happened if all individuals in our study population had had Graves' disease and had not been treated with RAI?

In the prediction models, the input variables would be set to values outlined in the scenarios 3 and 4 in Table 18.

Other scenarios could also be investigated. The results would be the difference between risk estimates for breast cancer incidence obtained in each scenario. Assuming that predictive models are correctly specified, using G-formula, we can obtain the unbiased mediation effect parameters.

Table 18 Values for variable inputs in breast cancer risk prediction models under several different intervention scenarios

Scenario	Hyperthyroidism etiology (E)	Surgery (0/1) (S)	RAI (0/1) (R)	ATDs (0/1) (A)	Uncontrolled hyperthyroidism (0/1) (U)	Iatrogenic hypothyroidism (0/1) (I)
1	1: Graves' disease	S_{E1}	R_{E1}	A_{E1}	$U_{E1, R1}$	$U_{E1, S1, R1}$
2	2: Toxic nodular goiter	S_{E2}	R_{E2}	A_{E2}	$U_{E2, R2}$	$U_{E2, S2, R2}$
3	1: Graves' disease	0	1	0	0	$U_{E1, S=0, R=1}$
4	1: Graves' disease	S_{E1}	0	A_{E1}	$U_{E1, R1}$	$U_{E1, S1, R=0}$

Appendices

Appendix 1 Potential confounding and modifying factors

A.1.1 Comorbidities

Supplementary table 1 Identification of individual comorbidities of interest

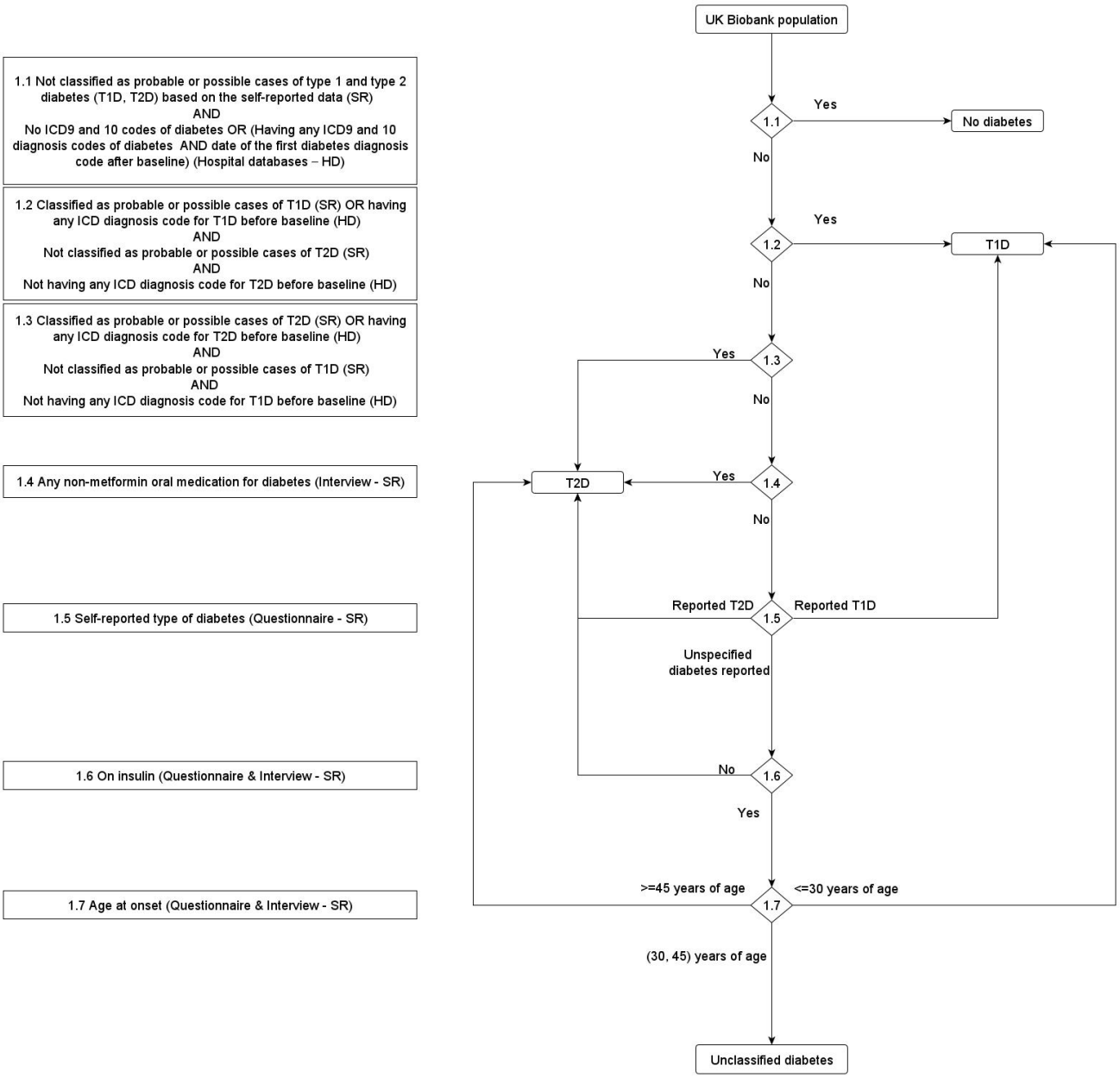
Risk factors	Coding	Visit at baseline	Information sources			
			Hospital inpatient databases[1]			
			ICD9	ICD10	OPCS3	OPCS4
Comorbidities						
- Obesity/Overweight	Yes No	BMI (PM): ≥25kg/m^2 (192)	NA	NA	NA	NA
-Type 2 diabetes	Yes No	See Supplementary table 2	See Supplementary table 2			
- Hypertension	Yes No	SR-I	401	I10	NA	NA
- Depression	Yes No	SR-I	2962, 2963, 311	F32, F33	NA	NA
- Autoimmune diseases	Yes No	See Supplementary table 3	See Supplementary table 3			

[1]: Include Hospital Episode Statistics Admitted Patient Care (England), Patient Episode Database for Wales Admitted Patient Care (Wales), and General Acute Inpatient and Day Case - Scottish Morbidity Record (Scotland)

Supplementary table 2 Self-reported, ICD-9 and ICD-10 codes for diabetes

Comorbidities		Visit at baseline	Hospital inpatient databases	
			ICD-9	ICD-10
Diabetes[1]	Type 1 diabetes	Algorithm developed by Eastwood et al., 2016 (134)	25001, 25011	E10
	Type 2 diabetes/unknown type of diabetes		250, 2500, 25000, 25009, 2501, 25010, 25019, 2502, 25020, 25021, 25029, 2503, 2504, 2509, 25099	E11, E12, E13, E14

1: See Supplementary figure 1 “Decision flowchart to identify and classify diabetes” for the final classification



Supplementary figure 1 Decision flowchart to identify and classify diabetes

Supplementary table 3 List of autoimmune diseases considered in the study

No	Conditions		Reported code	ICD-9	ICD-10	Note
1	Type 1 diabetes	Type 1 diabetes	See Supplementary table 2	See Supplementary table 2	See Supplementary table 2	
1	Inflammatory bowel disease	Inflammatory bowel disease	1461	555, 556	K50, K51	
2		Crohns disease	1462			
		Ulcerative colitis	1463			
3	Primary biliary cirrhosis	Primary biliary cirrhosis	1506	571.6	K743	
4	Sclerosing cholangitis	Sclerosing cholangitis	1475	576.1	K830	
5	Glomerulnephritis	Glomerulnephritis	1609	582	N03	
6	Adrenocortical insufficiency/Addison's disease	Adrenocortical insufficiency/Addison's disease	1234	255.4	E271	
7	Ankylosing spondylitis	Ankylosing spondylitis	1313	720	M45	
8	Rheumatoid arthritis	Rheumatoid arthritis	1464	714.0, 714.1, 714.2	M05, M06	
9	Psoriatic arthropathy	Psoriatic arthropathy	1477	696	M07	
10	Fibromyalgia	Fibromyalgia	1542	729.1	M797	
11	Psoriasis	Psoriasis	1453	696.0, 696.1	L40	
12	Pernicious anaemia	Pernicious anaemia	1331	281.0	D510	
13	Pemphigoid/pemphigus	Pemphigoid/pemphigus	1345	694.4, 694.5	L10, L12	
14	Vitiligo	Vitiligo	1661	709.01	L80	
15	Endometriosis	Endometriosis	1402	617	N80	
16	Sarcoidosis	Sarcoidosis	1371	135	D86	
17	Vasculitis	Vasculitis	1372	446.0, 446.4, 466.5, 725, 136.1, 446.21	M300, M310, M313, M315, M316, M317, M352, M353	
		Giant cell/temporal arteritis	1376			
		Polymyalgia rheumatica	1377			
		Wegners granulmatosis	1378			
		Microscopic polyarteritis	1379			
		Polyartertis nodosa	1380			
		Behcet’s syndrome	No corresponding code			

		Goodpasture’s syndrome	No corresponding code			
18	Systemic lupus erythematosis/sle	Systemic lupus erythematosis/sle	1381	710	M32	
19	Sjogren's syndrome/sicca syndrome	Sjogren's syndrome/sicca syndrome	1382	710.2	M350	
19	Dermatopolymyositis	Dermatopolymyositis	1383			
20		Dermatomyositis	1480	710.3, 710.4	M33	
		Polymyositis	1481			
21	Scleroderma/systemic sclerosis	Scleroderma/systemic sclerosis	1384	710.1	M34	
22	Raynaud's phenomenon/disease	Raynaud's phenomenon/disease	1561	443.0	I73.0	
23	Multiple sclerosis	Multiple sclerosis	1261	340	G35	
24	Malabsorption/coeliac disease	Malabsorption/coeliac disease	1456	579	K900	
25	Guillain–Barre´ syndrome	Acute infective polyneuritis/guillain-barre syndrome	1256	3570	G610	
26	Idiopathic fibrosing alveolitis	Fibrosing alveolitis/unspecified alveolitis	1122	51631	J84112	
27	Myasthenia gravis	Myasthenia gravis	1260, 1437	3580	G700	
28	Rheumatic fever/heart disease	Rheumatic fever	1479	390, 391, 392	I00, I01, I02	
29	Chagas disease	Chagas disease	No corresponding code	086.0, 086.1, 086.2	B57	
30	Autoimmune hemolytic anemia	Autoimmune hemolytic anemia	No corresponding code	2830	D590, D591	
31	Autoimmune thrombocytopenic purpura	Autoimmune thrombocytopenic purpura	No corresponding code	28731	D693	
32	Autoimmune hepatitis	Autoimmune hepatitis	No corresponding code	57142	K754	
33	Juvenile idiopathic arthritis	Juvenile idiopathic arthritis	No corresponding code	7143	M08	
34	Lambert–Eaton myasthenic syndrome	Lambert–Eaton myasthenic syndrome	No corresponding code	3583	G7080, G7081	
35	Autoimmune Myocarditis	Autoimmune Myocarditis	No corresponding code	No specific code	No specific code	Not included in the study
36	Polyendocrine syndromes	Polyendocrine syndromes	No corresponding code	2581	E310	
37	Relapsing polychondritis	Relapsing polychondritis	No corresponding code	No specific code	M941	
38	Uveitis	Uveitis	No corresponding code	3601	H4413	
39	Alopecia areata	Alopecia areata	No corresponding code	70400	L63	

ICD: International classification of diseases
Common autoimmune diseases were identified by including conditions in previous studies (27-29) and hand-searching in the UKB list of self-reported non-cancerous illnesses (Field 20002: https://biobank.ndph.ox.ac.uk/showcase/field.cgi?id=20002)

A.1.2 Breast cancer risk factors, lifestyle, healthcare-related and socioeconomic characteristics

Supplementary table 4 Definition of breast cancer risk factors, lifestyle, healthcare-related and socioeconomic characteristics

Risk factors	Coding	Information sources: Visit at baseline	Information sources: Hospital inpatient databases[1] ICD9	ICD10	OPCS3	OPCS4	Testing for confounding effect	Testing for effect modification
Hormone-related factors								
- Menopausal status	Premenopause Menopause before 51 years of age Menopause after 51 years of age	- Reporting menopause (periods stopped) (SR-Q) OR - Reporting use of menopausal hormone therapy (SR-Q) OR - Undergoing a bilateral oophorectomy (SR-I) OR - ≥51 years of age at baseline	NA	NA	Bilateral oophorectomy (6812)	Bilateral oophorectomy (Q221)	Yes	Yes
- Family history of breast cancer	Yes No	SR-Q	NA	NA	NA	NA	Yes	Yes
- Ever use of MHT	Never Yes, for less than 5 years Yes, for more than 5 years Yes, unknown duration Unknown	SR-Q	NA	NA	NA	NA	Yes	Yes
- Parity	No live birth One or two live births Three or more live births	SR-Q	NA	NA	NA	NA	Yes	Yes
- Age at first birth	No live birth Before 25 years of age Between 25-35 years of age After 35 years of age Unknown	SR-Q	NA	NA	NA	NA	Yes	Yes
- Ever use of oral contraception	Never Yes, for less than 10 years Yes, for more than 10 years Yes, unknown duration Unknown	SR-Q	NA	NA	NA	NA	Yes	Yes
- Age at menarche	≤11 years of age 12-14 years of age ≥15 years of age Unknown	SR-Q	NA	NA	NA	NA	Yes	Yes
Other risk factors								
- Physical activity[2]	Low Moderate High	SR-Q	NA	NA	NA	NA	Yes	Yes
- Alcohol consumption frequency	Never Once or twice a week or less Three times a week or more Unknown	SR-Q	NA	NA	NA	NA	Yes	No

- Smoking status	Never Former smoker Current smoker Unknown	SR-Q	NA	NA	NA	NA	Yes	No
- Race	White Asia Black and Caribbean Other or unknown	SR-Q	NA	NA	NA	NA	Yes	No
Health care-related factors and socioeconomic characteristics								
- Adherence to mammography guideline	<50 years of age >50 years of age, >3 years ago >50 years of age, in the last 3 years >50 years of age, never >50 years of age, unknown	SR-Q	NA	NA	NA	NA	Yes	No
- Adherence to cervical cancer screening guideline[3]	Never have a smear cervical test Ever have a smear cervical test, not adherence to guideline Ever have a smear cervical test, adherence to guideline Ever have a smear cervical test, >65 years of age Unknown	SR-Q	NA	NA	NA	NA	Yes	No
- Townsend score	Interquartile of Townsend score in the population study: ≤-3.668 (3.668, -2.206] (-2.206, -0.360] >0.360	UK data service	NA	NA	NA	NA	Yes	No
- Educational attainment	College or University degree A levels AS levels or equivalent O levels GCSEs CSEs or equivalent Other None of the above	SR-Q	NA	NA	NA	NA	Yes	No
- Occupation	Managers and Senior Officials Professional Occupations Associate Professional and Technical Occupations Administrative and Secretarial Occupations Skilled Trades Occupations Personal Service Occupations Sales and Customer Service Occupations Process, Plant and Machine Operatives Elementary Occupations Unknown	SR-Q	NA	NA	NA	NA	Yes	No

BMI: Body-mass index, HD: Hospital inpatient databases, ICD: International classification of diseases, NA: Not application, OPCS: OPCS Classification of Interventions and Procedures, PM: physical measurement, SR-I: Self-reported data - Interview with trained nurses, SR-Q: Self-reported data – Questionnaire

[1]: Include Hospital Episode Statistics Admitted Patient Care (England), Patient Episode Database for Wales Admitted Patient Care (Wales), and General Acute Inpatient and Day Case - Scottish Morbidity Record (Scotland)

[2]: Following IPAQ guideline (193)

[3]: Adherence to cervical cancer screening guideline was defined as having smear test in the last 3 years for women aged less than 50 years and in the last 5 years for women aged from 50-64 years

Appendix 2 Traditional approaches for mediation analysis

Considering again the simple situation presented in the main text (Figure 10).

The difference method consists of fitting two models:

- Model Y conditioning on X and Z: E[Y|X, Z] = $\beta_0 + \beta_1 a + \beta_3 z$ (1)
- Model Y conditioning on X, M, and Z: E[Y|X, Z] = $\beta_0' + \beta_1' a + \beta_2' m + \beta_3' z$ (2)

If the coefficient of X in the model (1) differs the coefficient of X in the model (2), it is regarded as an indication for mediating effect of M. The direct effect of X and the indirect effect of X through M are considered as β_1', and (β_1-β_1').

Similar to the difference method, the product method employed two models:

- Model Y conditioning on X, M, and Z: E[Y|X, Z] = $\beta_0'' + \beta_1'' a + \beta_2'' m + \beta_3'' z$ (3)
- Model M conditioning on X and Z: E[M|X, Z] = $\beta_0^* + \beta_1^* a + \beta_2^* z$ (4)

The direct effect of X and the indirect effect of X through M are considered as β_1^*, and the product of β_1^* and β_2'': (β_1^* β_2'').

Appendix 3 Different types of effect in causal mediation analysis

In a simple setting, suppose we have a binary exposure (with or without the exposure), a binary mediator (with or without the mediator), and an outcome Y, a demonstration of effect types, relevant research questions, and assumption is presented in the Supplementary table 5 (123).

In an individual perspective, a factual outcome is the outcome that occurred when an individual is exposed to their actual exposure condition, i.e the outcome that we can observe. A counterfactual outcome is the outcome that would have occurred if the individual was not exposed to the exposure that they actually have, i.e the outcome that we could not observed in the real, but a hypothetical world. Causality is established when the factual outcome differs from the counterfactual one. Following the same logic, the total causal effect of an exposure on a population is often defined as the difference between the probability of the outcome that would have occurred if all the population was exposed and the probability of the outcome that would have occurred if all the population was unexposed.

Supplementary table 5 A summary of the effects

Natural (in)direct effects – explaining the total effect	**Relevant research questions**	**Assumptions**
Total effect decompositions		
direct-indirect:	Does the effect of the exposure of interest include an indirect (mediated by the mediators) component?	(1) No uncontrolled confounding factors between the exposure – outcome, (2) No uncontrolled confounding factors between the exposure – mediator, (3) No uncontrolled confounding factors between mediator – outcome, (4) no confounding factors between mediator – outcome that are influenced by the exposure
indirect-direct:	Does the effect of the exposure of interest include a direct (not mediated by the mediators) component?	
both	What can we learn about the effect of the exposure of interest, either through mediators or through other mechanisms?	
Interventional effects – effects of hypothetically modified exposures or hypothetical interventions		
Several special effect types		
IDEs (paired with IIEs)	What is the effect of the exposure of interest when fixing the mediators at random values drawn from the conditional population without the exposure of interest?	(1) + (2) + (3)
IIEs (paired with IDEs)	What is the effect of the mediator of interest that is not caused by its ascendant?	(1) + (2) + (3)
CDEs	What is the effect of the exposure of interest when fixing the mediators at a certain value?	(1) + (2)
GIDEs: contain IDEs and CDEs as special cases	What is the effect of the exposure of interest when fixing the mediators at random values drawn from a given conditional population (not limited to population with and without the exposure of interest)?	(1) + (2) + (3)
Overall interventional effect	Decomposed by interventional direct-indirect effects or intervention indirect-direct effects	(1) + (2) + (3)
Total effect	Decomposed by natural (in)direct effects	(1) + (2) + (3) +(4)

NDE: Natural direct effect, NIE: Natural indirect effect, IDE: interventional direct effect, IIE: interventional indirect effect, CDE: Controlled direct effect, GIDEs: generalized interventional direct effects. Adapted version of the original table in (123).

Appendix 4 Directed acyclic graphs

Principal features of DAGs are summarized as following (194):

- Graphs are composed of nodes and arrows: Nodes represent variables, arrows connect nodes and represent relationship between them.
- Directed feature: Arrows from a node to another represent the assumed causal relationships between them, i.e. the first node causes the second. There is no bi-directed arrows in DAGs. Absence of arrows between nodes are a strong assumption as the causal relationships are assumed to not exist, which can cause bias with residual confounding if they actually exist
- Acyclic feature: No feedback loop, which means a variable cannot cause itself in a given population at a given time
- All potential variables that affect the intervention and the outcome should be included in DAGs, even when they are not observed
- Path: an acyclic sequence of adjacent nodes. Causal paths are the ones with all arrows pointing away from a node and into another one. Non-causal paths are the ones with at least one arrow going against the causal direction.

One way to interpret the causal relationship between the exposure X and the outcome Y conditioned on a set of confounding factors Z with DAGs is using backdoor criterion. Z fulfills the backdoor criterion if Z is not caused directly or indirectly by X and conditioning on Z blocks all the paths between X and Y that have an arrow into X. The total causal effect of X on Y is identifiable when conditioning on Z.

Backdoor criterion implies the confounder selection criterion (195). If there exist a set of observed covariates that meet the backdoor criterion, it is sufficient to condition on all observed pre-intervention covariates that either cause intervention, outcome, or both.

Appendix 5 Supplementary results of the systematic review and meta-analysis

A.5.1 Overall risk of bias of 20 studies included in the systematic review

Table 1. Risk of bias categorization based on number of point

	Maximum number of point	High RoB	Moderate RoB	Low RoB
Selection	4	<2	2	>2
Comparability	2	0	1	2
Exposure (case-control studies)	5	<3	3	>3
Outcome (cohort studies)	3	<2	2	>2

Table 2. Overall risk of bias of 20 studies included in the systematic review

Case-control studies													
Study	**Selection**					**Comparability**			**Exposure**					
	S1	**S2**	**S3**	**S4**	**Overall rating**	**C1**	**C2**	**Overall rating**	**E1**	**E2**	**E3**	**E4**	**E5**	**Overall rating**
Talamini, 1997	A	B	B	A	Moderate risk	–	–	High risk	C	A	A	B	A[5]	Moderate risk
Cristofanilli, 2005	A	A	A	A	Low risk	A	–	Moderate risk	B	A	A	B	A[6]	Moderate risk
Bach, 2020	B	B	B	A	High risk	–	–	High risk	A	A	A	B	B	Moderate risk
Cohort studies														
Study	**Selection**					**Comparability**			**Outcome**					
	S1	**S2**	**S3**	**S4**	**Overall rating**	**C1**	**C2**	**Overall rating**	**O1**	**O2**	**O3**			**Overall rating**
Munoz, 1978	D	B	A	B	High risk	–	–	High risk	D	A	D			High risk
Goldman, 1988	C	B	A	A	Moderate risk	–	–	High risk	B	A	D			High risk
Mellemgaard, 1998	C	A[6]	B	A	Moderate risk	–	–	High risk	A	A[6Erreur ! Signet non défini.]	B			Low risk

[5] Assumption based on the mean age and the age at Medicare initial enrollment period

[6] The authors used the national incidence rate to compare with the study cohort, which was also from national registries. We considered that they were in a same source

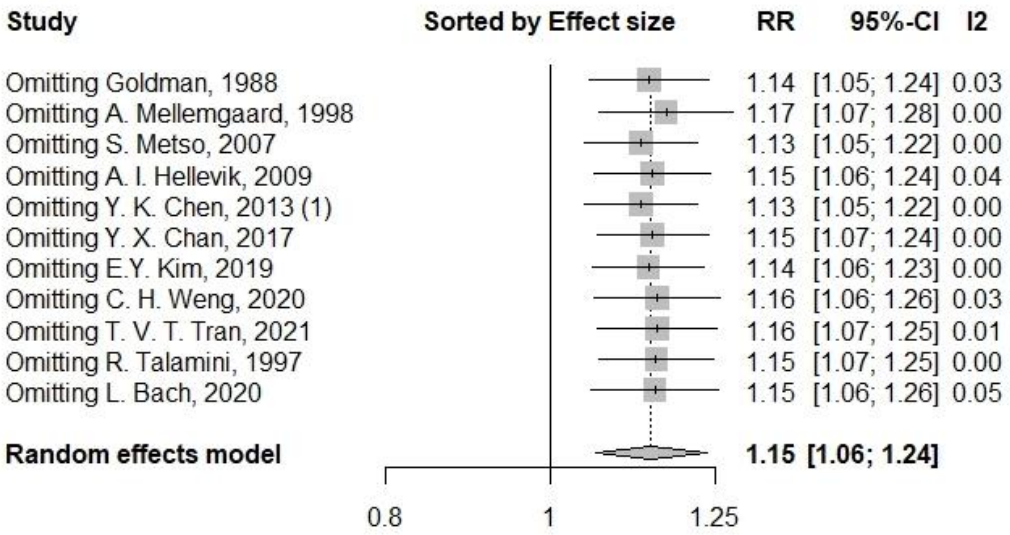
Metso, 2007	C	B	A	B	High risk	–	–	High risk	A	A	B	Low risk
Hellevik, 2009	C	A	A	B[7]	Moderate risk	–[8]	–	High risk	A	A	B	Low risk
Chen, 2013a	A	A	B	B[7]	Moderate risk	–	–	High risk	A	A[6]	B	Low risk
Chen, 2013b	A	A	B	B[7]	Moderate risk	–	–	High risk	A	A[6]	B	Low risk
Chan, 2017	C	A	A	A	Low risk	A[9]	B[9]	Low risk	A	A[6]	B	Low risk
Kim, 2019	C	A	A	B	Moderate risk	A	A	Low risk	C	A	C	High risk
Weng, 2020	C	A	C	B	High risk	A	A	Low risk	C	A	D	High risk
Tran, 2021	B	A	B	A	Low risk	A	A	Low risk	A	A	B	Moderate risk

[7] If the cancer of interest was breast or thyroid cancer for Chen, 2013a, colorectal or thyroid cancer for Chen, 2013b, prostate or lung cancer for Hellevik, 2009; thyroid cancer for Yeh, 2013, a point would be awarded to this item and the overall rating of Selection would be "low risk of bias"

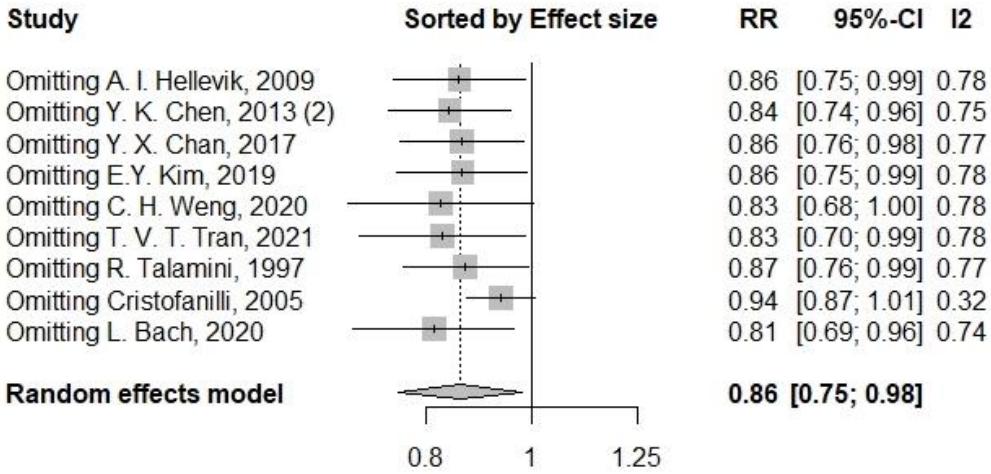
[8] If the cancer of interest was lung cancer, a point would be awarded to this item and the overall rating of Comparability would be "moderate risk of bias"

[9] Not adjusted for calendar year but all other important factors for thyroid, breast and respiratory tract cancers. If the cancer of interest was prostate cancer, the analysis was not adjusted for ethnicity and 1st-degree family history of cancer, no point would be awarded to the two items of "Comparability"

A.5.2 Influence analyses

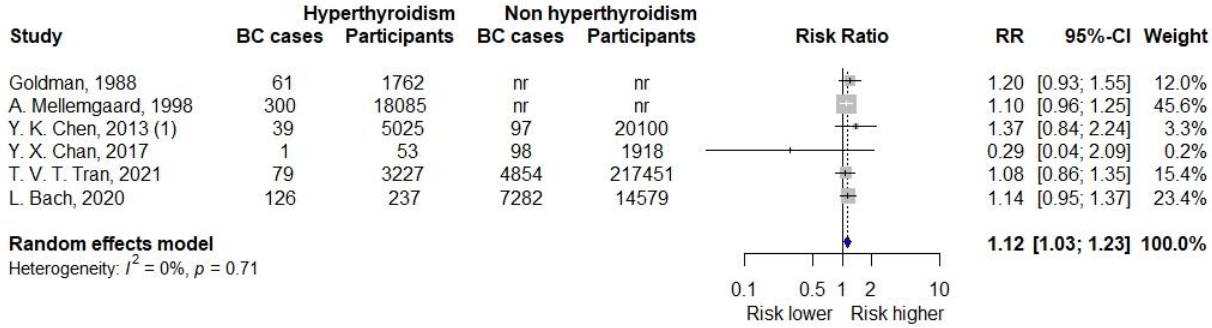


Supplementary figure 2 Influence analysis for the association between hyperthyroidism and breast cancer risk

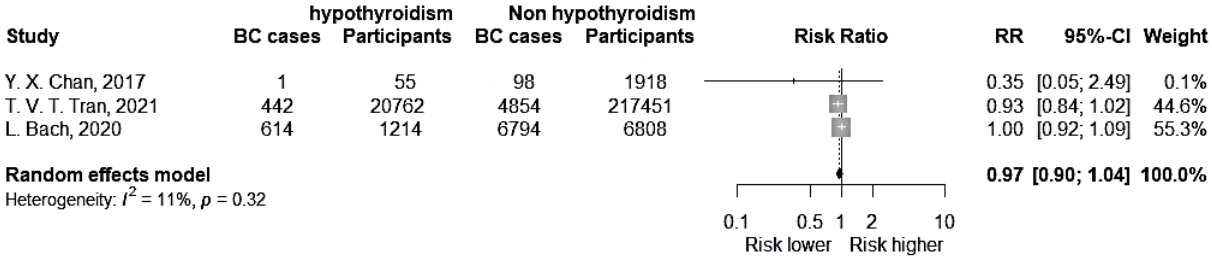


Supplementary figure 3 Influence analysis for the association between hypothyroidism and breast cancer risk

A.5.3 Sensitivity analyses on follow-up time



Supplementary figure 4 Forest plot for the association between hyperthyroidism and breast cancer risk when including studies with available risk estimates after at least one year of follow-up



Supplementary figure 5 Forest plot for the association between hypothyroidism and breast cancer risk when including studies with available risk estimates after at least one year of follow-up

Appendix 6 Supplementary methods for the chapter V

Breast dose reconstruction

Time-integrated activity coefficients (MBq.h/MBq) used to reconsctruct internal dose from RAI for the source regions incorporating RAI in withdrawal and rhTSH patients treated for thyroid cancer. SD: standard deviation. Data derived from Rémy et al (2008) (107).

Organ or tissue	**Time-integrated activity coefficient ((MBq.h)/MBq, mean ± SD)**	
	Withdrawal patients n=19	**rhTSH patients n=11**
Stomach	5.3 ± 1.8	1.5 ± 0.8
Colon	2.9 ± 1.9	4.0 ± 1.0
Urinary bladder	1.4 ± 0.7	1.3 ± 0.2
Rest of the body	20.3 ± 13.7	12.8 ± 3.1

We did not have information on methods of preparation for RAI treatment (i.e. rhTSH or thyroid hormone withdrawal). However, since rhTSH was first approved as an adjunct for RAI in Europe in 2005, it is probable that RAI treatment was mostly after thyroid hormone withdrawal in our study. Hence we used the time-integrated activity coefficients estimated for withdrawal patients.

Person year table details

For the analyses in our study, cases and person-years were stratified on the following factors:

Factor	Categories	Category definitions
Attained age[a]	18	Five year categories from 0 through 95
Calendar period	47	1990-1969, and individual year categories from 1970 through 2015
Age at thyroid cancer diagnosis	4	<30, 30-40, 40-50, ≥50 years of age
Year at diagnosis	3	≤1960, 1960-1980, >1980
Cohort	3	French, Italian, Swedish cohorts
Time of follow-up[a]	3	≤10, 10-20, >20 years
Number of therapeutic RAI administration[a]	2	0, 1, >1
Maximum RAI activity in a single administration[a]	5	Never exposed, <40, 40-100, 100-200, 200-400, ≥400
Lag 5 breast dose from RAI (mCi)[a]	5	Never exposed, <40, 40-100, 100-200, 200-400, ≥400
Lag 10 breast dose from RAI (mCi)[a]	5	Never exposed, <40, 40-100, 100-200, 200-400, ≥400
Lag 5 breast dose from external radiotherapy (mGy)[a]	5	Never exposed, <1000, 1000-10000, ≥10000
Lag 10 breast dose from external radiotherapy (mGy)[a]	5	Never exposed, <1000, 1000-10000, ≥10000

[a] Time-dependent categories

Risk models

Background rate of the pooled population was formulated as following:

$$\text{Background rate} = \text{erate} * \lambda_0(a, c, x), \text{ in which}$$

- erate denotes the expected rate from the external references at a certain age and a certain calendar period
- $\lambda_0(a, c, x)$ expressed further adjustment of the background rate on age at diagnostic (a: <30/30-40/40-50/≥50 years of age), cohort (c: France/Sweden/Italy), and cumulative dose of external radiotherapy (x: 0/ <1000/ 1000-10000/ ≥10000 mGy) (except stated otherwise).

We compared models with and without interactions between the covariates a, c, and x by evaluating AIC values and the final models had the following form:

$$\lambda_0(a, c, x) = exp(a + c + x).$$

The ERR formulation of the exposed incidence rate has the form

$$\text{ERR} = \text{erate} * \lambda_0(a, c, x) * [1 + \rho(d) * f(z)], \text{ in which}$$

- ρ(d) describes the shape of the dose-response depending on the cumulative RAI activity (d). Using likelihood ratio test, we evaluated linear (βd), linear-quadratic ($\beta_1 d + \beta_2 d^2$), linear-exponential(linear) ($\beta_1 d * \exp(\beta_2 d)$) and linear-exponential(quadratic) ($\beta_1 d * \exp(\beta_2 d^2)$) models for

dose-response shape. We found no evidence of non-linearity in the dose-response analyses and used linear models in the final models.

- f(z) describes the effect of modifying factors on the RAI effect.

Linear threshold models

We used the same model from the ERR analyses for the evaluation of linear threshold models. Specifically, a linear threshold model was evaluated repeatedly for a wide range of possible values d0 of the unknown threshold dTH. In the linear threshold model, dTH = d - d0 if d>d0 and dTH=0 if d≤d0. We compared deviances to identify the maximum log-likelihood estimate for the threshold. The 95%CI of the threshold was determined by including all values for which the 2 times the log likelihood drops off by no more than 3.84 (i.e., the value of the Chi-square statistic with one degree of freedom at α=0.05). The upper limit of the 95%CI indicates the maximum threshold value that is compatible with the data.

Appendix 7 Inverse probability weighting

To obtain the risk estimates from the inverse probability-weighted Poisson model, we adapted a previously proposed method (196, 197), involving two steps.

In the first step, time since diagnosis was divided into years since thyroid cancer diagnosis (range: 2-67 years). Using separate logistic regression models, weights were estimated for the probability of exposure to RAI, the probability of exposure to external radiotherapy and the probability of not lost of follow-up at a given time. We calculated weights for the exposure of RAI and external radiotherapy, separately, by fitting logistic regression models for both the numerator and denominator. The models of for the numerator had country and time since diagnosis, whereas the models for the denominator included country, time since diagnosis, age and year at thyroid cancer diagnosis. Time since diagnosis, age and year at thyroid cancer diagnosis were included as continuous variables using restricted quadratic splines with four knots placed at the 5^{th}, 35^{th}, 65^{th}, and 95^{th} percentiles (198). For the non-lost of follow-up weights, using pooled logistic regression, the model for the numerator included country, time since diagnosis (restricted quadratic splines), cumulative activities of RAI at a given time (time-depending variable), cumulative doses of external radiotherapy at a given time (time-depending variable), whereas the model for the denominator included country, time since diagnosis (restricted quadratic splines), age and year at thyroid cancer diagnosis (restricted quadratic splines), cumulative activities of RAI at a given time (time-depending variable), and cumulative doses of external radiotherapy at a given time (time-depending variable). In the pooled logistic regression model, the weights were cumulatively multiplied for each person. The final weight of a patients in a given year were calculated by multiplying the weights of exposure to RAI, external radiotherapy, and non-lost of follow-up. We truncated the final weights at the first and the 99^{th} percentiles to avoid extreme weights that could lead to imprecise effect estimates. The final estimated weights had a mean of 0.86 (standard deviation=0.50, range: 0.17 to 3.38).

In the second step, we built an ungrouped person-year table and the inverse probability-weighted Poisson models were fit as described in the main text, by weighting participants according to their estimated weights. We were not able to account for potential replications of patients induced by inverse probability weighting or bootstrap (197, 199), therefore, we presented the results calculated with the naïve model-based variance estimator from the maximum partial likelihood estimator, which resulted in unbiased risk estimates but biased 95% CIs (197, 199).

Appendix 8 Supplementary results for the chapter V

Supplementary table 6 Characteristics of the pooled cohort according to therapeutic RAI

	Radioactive iodine therapy (N=5,292)	**No radioactive iodine therapy** (N=3,183)	**P-value**[1]
Year of treatment, year, median (min-max)	1990 (1935-2005)	1984 (1934-2005)	<0.001
Age at thyroid cancer diagnosis, year, mean (SD)	45.0 (15.5)	43.9 (15.2)	0.230
Follow-up time, year, median (min-max)	12 (2.1-55.2)	14.1 (2-66.5)	<0.001
Breast cancer cases, n (%)	176 (3.3)	159 (5)	<0.001
Time to breast cancer, year, median (min-max)	12.0 (2.2-46)	17.9 (2.0-55.2)	0.001
Ionising radiation for thyroid cancer			
External radiotherapy, n (%)	525 (9.9)	445 (14)	<0.001
Diagnostic RAI activity, n (%)	1393 (26.3)	521 (16.4)	<0.001
- Number of diagnostic RAI activity, median (min-max)	2 (1-23)	3 (1-21)	0.291
- Cumulative activity of diagnostic RAI, mCi, median (min-max)	7.0 (0.0-57)	3.1 (0.1-25)	<0.001
Cumulative radiation dose delivered to the breast			
Diagnostic RAI activity, mGy, median (min-max)[2]	17.3 (0-140.7)	8.0 (0.1-61.7)	<0.001
External radiotherapy, mGy, median (min-max)	936 (1.0-46,594)	328 (1.5-46,595)	<0.001
- Imputed dosimetry for external radiotherapy, n (%)	184 (35)	283 (64)	<0.001

SD: Standard deviation
[1] P-value of t-test, Mann-Whitney U test and $\chi 2$ test, where appropriate
[2] Patients aged >15 years at thyroid cancer diagnosis

Supplementary table 7 Sensitivity analyses for breast cancer risk associated with therapeutic RAI (ten-year latency time), lost of follow-up as the main outcome

	Lost of follow-up as outcome	
	Lost of follow-up	**RR[1] (95%CI)**
Therapeutic RAI activity[3]		
No	1911/51,115	1
Yes	3793/62,286	1.16 (1.10-1.23)
P-heterogeneity		*<0.001*
Cumulative activity of therapeutic RAI (mCi)		
No RAI treatment		
<40	1911/51,115	1
40-100	127/3,761	0.87 (0.72-1.03)
100-200	335/1,114	1.04 (0.92-1.17)
200-400	2453/33,544	1.23 (1.16-1.31)
≥400	662/10,087	1.10 (1.00-1.20)
P-heterogeneity	216/3,780	1.05 (0.91-1.21)
P-trend		*<0.001*
ERR per 100 mCi[1]		*0.083*

CI: Confidence interval, ERR: Excess relative risk, RR: Relative risk

[1] Stratified by country, age at diagnosis, and dose of external radiotherapy delivered to the breast in the background risks

Supplementary table 8 Breast cancer risk associated with therapeutic RAI activities (10-year latency time) stratified by population characteristics

	The pooled population (n=8,475) RAI treatment vs no RAI treatment		
	Breast cancer cases RAI/No RAI	**RR (95%CI)**	**ERR per 100 mCi[1]**
External radiotherapy[2]			
No	89/211	1.06 (0.82-1.35)	0.15 (0.02-0.37)
Yes	12/23	1.14 (0.55-2.25)	0.24 (?-1.00)
p-interaction[3]		*>0.5*	
Age at thyroid cancer diagnosis (year)[4]			
<30	26/35	1.48 (0.87-2.50)	0.33 (0.07-0.96)
30-40	26/62	0.97 (0.60-1.52)	0.08 (?-0.46)
40-50	23/64	0.83 (0.50-1.31)	0.13 (?-0.57)
≥50	26/73	1.20 (0.75-1.85)	0.16 (?-0.67)
p-interaction[3]		*>0.5*	
Year at thyroid cancer diagnosis[5]			
≤1960	7/27	1.38 (0.55-3.03)	0.18 (?-0.84)
1960-1980	41/85	1.01 (0.69-1.46)	0.18 (?-0.51)
>1980	53/122	1.01 (0.73-1.40)	0.16 (?-0.44)
p-interaction[3]		*>0.5*	
Follow-up time (years)[5]			
≤15	35/142	1.04 (0.71-1.49)	0.04 (?-0.36)
15-20	19/20	0.96 (0.51-1.81)	0.05 (?-0.39)
>20	47/72	1.06 (0.72-1.54)	0.32 (0.08-0.68)
p-interaction[3]		*0.234*	

CI: Confidence interval, AR: Absolute risk, RR: Relative risk

[1] When the lower bound cannot be estimated, a question mark '?' was reported

[2] Adjusted for country, and age at diagnosis, in the background risks

[3] p-interaction was computed by testing the statistical significance of an interaction term between radioactive iodine and the studied covariate (likelihood-ratio χ^2 tests)

[4] Adjusted for country, and dose of external radiotherapy delivered to the breast in the background risks

[5] Adjusted for country, age at diagnosis, and dose of external radiotherapy delivered to the breast in the background risks

Supplementary table 9 Sensitivity analyses for breast cancer risk associated with therapeutic RAI (ten-year latency time)

	Accounting for both diagnostic and therapeutic RAI		Censoring patients at ten years after external radiotherapy		New endpoint for the Italian and French cohorts[2]		IPW
	BC cases	**RR[1] (95%CI)**	**BC cases**	**RR[1] (95%CI)**	**BC cases**	**RR[1] (95%CI)**	**RR[1] (95%CI)**
Therapeutic RAI activity[3]							
No	200/78,456	1	210/80,019	1	223/82,969	1	1
Yes	135/34,945	1.17 (0.93-1.46)	88/24,669	1.0 (0.91-1.47)	81/24,196	1.11 (0.87-1.42)	1.30 (1.00-1.67)
P-heterogeneity		*0.192*		*0.229*		*0.392*	*0.049*
Cumulative activity of therapeutic RAI (mCi)[3]							
No RAI treatment	200/78,456	1	210/80,019	1	223/82,696	1	1
<40	38/9,492	1.21 (0.82-1.73)	4/2,273	0.50 (0.15-1.18)	4/2,167	0.52 (0.16-1.24)	0.38 (0.06-1.22)
40-100	16/6,539	0.79 (0.45-1.29)	15/5,343	0.92 (0.52-1.53)	15/6,150	0.76 (0.43-1.25)	0.92 (0.47-1.63)
100-200	53/14,043	1.15 (0.83-1.55)	47/12,970	1.05 (0.75-1.43)	40/11,842	0.99 (0.70-1.38)	1.30 (0.95-1.76)
200-400	18/3,716	1.56 (0.92-2.50)	16/3,222	1.47 (0.84-2.40)	13/3,110	1.28 (0.69-2.17)	2.27 (1.40-3.49)
≥400	10/1,155	2.80 (1.35-5.17)	6/861	2.03 (0.78-4.31)	9/926	2.92 (1.36-5.51)	1.67 (0.41-4.44)
P-heterogeneity		*0.054*		*0.236*		*0.053*	*0.009*
P-trend		*0.027*		*0.096*		*0.073*	*0.004*
ERR per 100 mCi[1]		0.17 (0.02-0.37)		0.14 (-0.02-0.36)		0.14 (-0.01-0.34)	0.31 (0.09-0.61)
Cumulative activity of therapeutic RAI (mGy)[3~~4]							
No RAI treatment	200/76,393	1	208/77,621	1	221/80,441	1	1
<100	37/9,286	1.14 (0.78-1.64)	5/2,619	0.55 (0.19-1.20)	5/2,479	0.58 (0.20-1.26)	0.41 (0.08-1.21)
100-250	36/11,217	0.99 (0.68-1.40)	45/14,767	0.93 (0.65-1.24)	42/14,651	0.85 (0.60-1.17)	1.13 (0.82-1.54)
250-500	32/9,476	1.00 (0.67-3.19)	19/4,280	1.32 (0.79-2.07)	14/3,929	1.05 (0.58-1.74)	1.60 (0.99-2.44)
500-1,000	17/2,624	1.97 (1.14-4.32)	13/1,721	2.22 (1.19-3.79)	12/1,697	2.13 (1.11-3.70)	3.09 (1.77-5.05)
≥1,000	6/869	2.04 (0.79-1.64)	2/511	1.09 (0.18-3.48)	3/572	1.48 (0.36-3.95)	0.91 (0.06-3.91)
P-heterogeneity		*0.168*		*0.072*		*0.130*	*0.002*
P-trend		*0.089*		*0.205*		*0.236*	*0.005*
ERR per 100 mGy[1]		0.05 (0.00-0.14)		0.05 (-0.02-0.14)		0.04 (-0.02-0.12)	0.12 (0.03-0.24)

BC: Breast cancer, CI: Confidence interval, ERR: Excess relative risk, IPW: Inverse probability weighting, RR: Relative risk

[1] Adjusted for country, age at diagnosis, and dose of external radiotherapy delivered to the breast in the background risks

[2] 31/12/2003 for Italian cohort and 31/12/2009 for French cohort

[3] Except for the analysis accounting for both diagnostic and therapeutic RAI, which showed results of 'ever received any RAI activity' and 'cumulative activity/dose of any RAI administration delivered to the breast

[4] Analysis conducted among women aged >15 years at thyroid cancer diagnosis

Supplementary table 10 ERR estimates for breast cancer incidence in previous studies

Reference	Cases	Dose		ERR/100Gy	
		Average	Max	ERR	95%CI
Travis 2003 (200)	105	25 Gy	61 Gy	0.015	(0.004–0.073)
Guibout 2005 (201)	16	5 Gy	80 Gy	0.013	(<0–0.075)
Preston 2007 (181)	1073	NA	4Gy	0.087	0.055-0.13[1]
Inskip 2009 (202)	107	14 Gy	60 Gy	0.027	(0.010–0.067)
Davis 2015 (183)	118	60 mGy (0-960 mGy)[2]	NA	0.19	-0.06-0.61
Preston 2016 (180)	1922	37mGy	~1Gy	0.07	-0.005-0.19
Brenner 2018 (182)	1470	NA	4Gy	0.112	0.073-0.159

[1] 90%CI
[2] Whole body

References

1. Melmed S, Polonsky KS, Larsen PR, Kronenberg HM. Williams Textbook of Endocrinology E-Book: Elsevier Health Sciences; 2015.
2. Boron WF, Boulpaep EL. Medical Physiology A Cellular and Molecular Approach, Updated 2nd Ed: Elsevier Health Sciences; 2016.
3. Coscia F, Taler-Verčič A, Chang VT, Sinn L, O'Reilly FJ, Izoré T, et al. The structure of human thyroglobulin. Nature. 2020;578(7796):627-30.
4. Davis PJ, Goglia F, Leonard JL. Nongenomic actions of thyroid hormone. Nature reviews Endocrinology. 2016;12(2):111-21.
5. Norman AW, Litwack G. CHAPTER 6 - Thyroid Hormones. In: Norman AW, Litwack G, editors. Hormones (Second Edition). San Diego: Academic Press; 1997. p. 169-91.
6. Chaker L, Bianco AC, Jonklaas J, Peeters RP. Hypothyroidism. Lancet (London, England). 2017;390(10101):1550-62.
7. De Leo S, Lee S, Braverman L. Hyperthyroidism. Lancet (London, England). 2016;388(10047):906-18.
8. Cooper DS, Biondi B. Subclinical thyroid disease. Lancet (London, England). 2012;379(9821):1142-54.
9. Ross DS, Burch HB, Cooper DS, Greenlee MC, Laurberg P, Maia AL, et al. 2016 American Thyroid Association guidelines for diagnosis and management of hyperthyroidism and other causes of thyrotoxicosis. Thyroid. 2016;26(10):1343-421.
10. Garber JR, Cobin RH, Gharib H, Hennessey JV, Klein I, Mechanick JI, et al. Clinical practice guidelines for hypothyroidism in adults: cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association. Thyroid. 2012;22(12):1200-35.
11. Taylor PN, Albrecht D, Scholz A, Gutierrez-Buey G, Lazarus JH, Dayan CM, et al. Global epidemiology of hyperthyroidism and hypothyroidism. Nature reviews Endocrinology. 2018;14(5):301-16.
12. Garmendia Madariaga A, Santos Palacios S, Guillén-Grima F, Galofré JC. The Incidence and Prevalence of Thyroid Dysfunction in Europe: A Meta-Analysis. The Journal of Clinical Endocrinology & Metabolism. 2014;99(3):923-31.
13. Hollowell JG, Staehling NW, Flanders WD, Hannon WH, Gunter EW, Spencer CA, et al. Serum TSH, T4, and Thyroid Antibodies in the United States Population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). The Journal of Clinical Endocrinology & Metabolism. 2002;87(2):489-99.

14. Vanderpump MPJ. The epidemiology of thyroid disease. British Medical Bulletin. 2011;99(1):39-51.

15. Fine JP, Gray RJ. A Proportional Hazards Model for the Subdistribution of a Competing Risk. Journal of the American Statistical Association. 1999;94(446):496-509.

16. Vaidya B, Pearce SH. Diagnosis and management of thyrotoxicosis. Bmj. 2014;349:g5128.

17. Franklyn JA, Boelaert K. Thyrotoxicosis. Lancet. 2012;379(9821):1155-66.

18. Goichot B, Caron P, Landron F, Bouée S. Clinical presentation of hyperthyroidism in a large representative sample of outpatients in France: relationships with age, aetiology and hormonal parameters. Clinical endocrinology. 2016;84(3):445-51.

19. Boelaert K, Torlinska B, Holder RL, Franklyn JA. Older subjects with hyperthyroidism present with a paucity of symptoms and signs: a large cross-sectional study. The Journal of clinical endocrinology and metabolism. 2010;95(6):2715-26.

20. Jabbar A, Pingitore A, Pearce SH, Zaman A, Iervasi G, Razvi S. Thyroid hormones and cardiovascular disease. Nature reviews Cardiology. 2017;14(1):39-55.

21. Brandt F, Thvilum M, Almind D, Christensen K, Green A, Hegedüs L, et al. Morbidity before and after the diagnosis of hyperthyroidism: a nationwide register-based study. PloS one. 2013;8(6).

22. Chen R-H, Chen H-Y, Man K-M, Chen S-J, Chen W, Liu P-L, et al. Thyroid diseases increased the risk of type 2 diabetes mellitus: A nation-wide cohort study. Medicine. 2019;98(20).

23. Bardugo A, Derazne E, Zucker I, Bendor CD, Puris G, Lutski M, et al. Adolescent Thyroid Disorders and Risk for Type 2 Diabetes in Young Adulthood. The Journal of Clinical Endocrinology & Metabolism. 2021;106(9):e3426-e35.

24. Fallahi P, Ferrari SM, Ruffilli I, Elia G, Biricotti M, Vita R, et al. The association of other autoimmune diseases in patients with autoimmune thyroiditis: Review of the literature and report of a large series of patients. Autoimmunity reviews. 2016;15(12):1125-8.

25. Ferrari SM, Fallahi P, Ruffilli I, Elia G, Ragusa F, Benvenga S, et al. The association of other autoimmune diseases in patients with Graves' disease (with or without ophthalmopathy): Review of the literature and report of a large series. Autoimmunity reviews. 2019;18(3):287-92.

26. Boelaert K, Newby PR, Simmonds MJ, Holder RL, Carr-Smith JD, Heward JM, et al. Prevalence and relative risk of other autoimmune diseases in subjects with autoimmune thyroid disease. The American journal of medicine. 2010;123(2):183.e1-9.

27. Antonelli A, Benvenga S. Editorial: The Association of Other Autoimmune Diseases in Patients With Thyroid Autoimmunity. Frontiers in endocrinology. 2018;9(540).

28. Krassas GE, Poppe K, Glinoer D. Thyroid Function and Human Reproductive Health. Endocrine reviews. 2010;31(5):702-55.

29. Cooper D, Braverman L, Utiger R. Werner and Ingbar's the thyroid: a fundamental and clinical text. 2004.

30. Pearce SH. Spontaneous reporting of adverse reactions to carbimazole and propylthiouracil in the UK. Clinical endocrinology. 2004;61(5):589-94.

31. Ross DS, Burch HB, Cooper DS, Greenlee MC, Laurberg P, Maia AL, et al. 2016 American Thyroid Association Guidelines for Diagnosis and Management of Hyperthyroidism and Other Causes of Thyrotoxicosis. Thyroid : official journal of the American Thyroid Association. 2016;26(10):1343-421.

32. Vaidya B, Williams GR, Abraham P, Pearce SH. Radioiodine treatment for benign thyroid disorders: results of a nationwide survey of UK endocrinologists. Clinical endocrinology. 2008;68(5):814-20.

33. Franklyn JA. Management guidelines for hyperthyroidism. Bailliere's clinical endocrinology and metabolism. 1997;11(3):561-71.

34. Bartalena L, Burch HB, Burman KD, Kahaly GJ. A 2013 European survey of clinical practice patterns in the management of Graves' disease. Clinical endocrinology. 2016;84(1):115-20.

35. Vasileiou M, Gilbert J, Fishburn S, Boelaert K. Thyroid disease assessment and management: summary of NICE guidance. BMJ. 2020;368:m41.

36. Biondi B, Cappola AR, Cooper DS. Subclinical Hypothyroidism: A Review. Jama. 2019;322(2):153-60.

37. Biondi B, Cooper DS. Thyroid hormone therapy for hypothyroidism. Endocrine. 2019;66(1):18-26.

38. Laurberg P, Knudsen N, Andersen S, Carlé A, Pedersen IB, Karmisholt J. Thyroid function and obesity. European thyroid journal. 2012;1(3):159-67.

39. Chaker L, Ligthart S, Korevaar TI, Hofman A, Franco OH, Peeters RP, et al. Thyroid function and risk of type 2 diabetes: a population-based prospective cohort study. BMC Med. 2016;14(1):150.

40. Biondi B, Kahaly GJ, Robertson RP. Thyroid dysfunction and diabetes mellitus: two closely associated disorders. Endocrine reviews. 2019;40(3):789-824.

41. Gronich N, Deftereos SN, Lavi I, Persidis AS, Abernethy DR, Rennert G. Hypothyroidism is a Risk Factor for New-Onset Diabetes: A Cohort Study. Diabetes care. 2015;38(9):1657-64.

42. Ettleson MD, Bianco AC. Individualized Therapy for Hypothyroidism: Is T4 Enough for Everyone? The Journal of Clinical Endocrinology & Metabolism. 2020;105(9):e3090-e104.

43. Jonklaas J, Bianco AC, Cappola AR, Celi FS, Fliers E, Heuer H, et al. Evidence-Based Use of Levothyroxine/Liothyronine Combinations in Treating Hypothyroidism: A Consensus Document. Thyroid : official journal of the American Thyroid Association. 2021;31(2):156-82.

44. Hercbergs A, Mousa SA, Leinung M, Lin H-Y, Davis PJ. Thyroid hormone in the clinic and breast cancer. Hormones and Cancer. 2018;9(3):139-43.

45. Moeller LC, Führer D. Thyroid hormone, thyroid hormone receptors, and cancer: a clinical perspective. Endocrine-related cancer. 2013;20(2):R19-29.

46. Hellevik AI, Asvold BO, Bjøro T, Romundstad PR, Nilsen TI, Vatten LJ. Thyroid function and cancer risk: a prospective population study. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2009;18(2):570-4.

47. Khan SR, Chaker L, Ruiter R, Aerts JG, Hofman A, Dehghan A, et al. Thyroid Function and Cancer Risk: The Rotterdam Study. The Journal of clinical endocrinology and metabolism. 2016;101(12):5030-6.

48. Yeh NC, Chou CW, Weng SF, Yang CY, Yen FC, Lee SY, et al. Hyperthyroidism and thyroid cancer risk: a population-based cohort study. Experimental and clinical endocrinology & diabetes : official journal, German Society of Endocrinology [and] German Diabetes Association. 2013;121(7):402-6.

49. Krashin E, Silverman B, Steinberg DM, Yekutieli D, Giveon S, Fabian O, et al. Opposing effects of thyroid hormones on cancer risk: a population-based study. European journal of endocrinology. 2021;184(3):477-86.

50. Ryödi E, Metso S, Jaatinen P, Huhtala H, Saaristo R, Välimäki M, et al. Cancer Incidence and Mortality in Patients Treated Either With RAI or Thyroidectomy for Hyperthyroidism. The Journal of clinical endocrinology and metabolism. 2015;100(10):3710-7.

51. Ron E, Doody MM, Becker DV, Brill AB, Curtis RE, Goldman MB, et al. Cancer mortality following treatment for adult hyperthyroidism. Cooperative Thyrotoxicosis Therapy Follow-up Study Group. Jama. 1998;280(4):347-55.

52. Metso S, Jaatinen P, Huhtala H, Auvinen A, Oksala H, Salmi J. Increased cardiovascular and cancer mortality after radioiodine treatment for hyperthyroidism. The Journal of clinical endocrinology and metabolism. 2007;92(6):2190-6.

53. Zhang Y, Chang Y, Ryu S, Cho J, Lee WY, Rhee EJ, et al. Thyroid hormones and mortality risk in euthyroid individuals: the Kangbuk Samsung health study. The Journal of clinical endocrinology and metabolism. 2014;99(7):2467-76.

54. Tran TV, Kitahara CM, de Vathaire F, Boutron-Ruault MC, Journy N. Thyroid dysfunction and cancer incidence: a systematic review and meta-analysis. Endocrine-related cancer. 2020.

55. Kitahara CM, Preston DL, Sosa JA, Berrington de Gonzalez A. Association of Radioactive Iodine, Antithyroid Drug, and Surgical Treatments With Solid Cancer Mortality in Patients With Hyperthyroidism. JAMA Netw Open. 2020;3(7):e209660.

56. Krashin E, Silverman B, Steinberg DM, Yekutieli D, Giveon S, Fabian O, et al. Opposing effects of thyroid hormones on cancer risk: a population-based study. European journal of endocrinology. 2021;184(3):477-86.

57. Franceschi S, Preston-Martin S, Dal Maso L, Negri E, La Vecchia C, Mack WJ, et al. A pooled analysis of case-control studies of thyroid cancer. IV. Benign thyroid diseases. Cancer causes & control : CCC. 1999;10(6):583-95.

58. Rinaldi S, Plummer M, Biessy C, Tsilidis KK, Østergaard JN, Overvad K, et al. Thyroid-Stimulating Hormone, Thyroglobulin, and Thyroid Hormones and Risk of Differentiated Thyroid Carcinoma: The EPIC Study. JNCI: Journal of the National Cancer Institute. 2014;106(6).

59. Beatson GT. On the Treatment of Inoperable Cases of Carcinoma of the Mamma: Suggestions for a New Method of Treatment, with Illustrative Cases. Transactions Medico-Chirurgical Society of Edinburgh. 1896;15:153-79.

60. Goemann IM, Romitti M, Meyer ELS, Wajner SM, Maia AL. Role of thyroid hormones in the neoplastic process: an overview. Endocrine-related cancer. 2017;24(11):R367-r85.

61. Liu YC, Yeh CT, Lin KH. Molecular Functions of Thyroid Hormone Signaling in Regulation of Cancer Progression and Anti-Apoptosis. International journal of molecular sciences. 2019;20(20).

62. Lin HY, Chin YT, Shih YJ, Chen YR, Leinung M, Keating KA, et al. In tumor cells, thyroid hormone analogues non-immunologically regulate PD-L1 and PD-1 accumulation that is anti-apoptotic. Oncotarget. 2018;9(75):34033-7.

63. Dong L, Lu J, Zhao B, Wang W, Zhao Y. Review of the possible association between thyroid and breast carcinoma. World journal of surgical oncology. 2018;16(1):130.

64. Tosovic A, Becker C, Bondeson AG, Bondeson L, Ericsson UB, Malm J, et al. Prospectively measured thyroid hormones and thyroid peroxidase antibodies in relation to breast cancer risk. International journal of cancer. 2012;131(9):2126-33.

65. Kim EY, Chang Y, Lee KH, Yun JS, Park YL, Park CH, et al. Serum concentration of thyroid hormones in abnormal and euthyroid ranges and breast cancer risk: A cohort study. International journal of cancer. 2019;145(12):3257-66.

66. Tosovic A, Bondeson AG, Bondeson L, Ericsson UB, Malm J, Manjer J. Prospectively measured triiodothyronine levels are positively associated with breast cancer risk in postmenopausal women. Breast cancer research : BCR. 2010;12(3):R33.

67. Brandt J, Borgquist S, Manjer J. Prospectively measured thyroid hormones and thyroid peroxidase antibodies in relation to risk of different breast cancer subgroups: a Malmö Diet and Cancer Study. Cancer causes & control : CCC. 2015;26(8):1093-104.

68. Ortega-Olvera C, Ulloa-Aguirre A, Ángeles-Llerenas A, Mainero-Ratchelous FE, González-Acevedo CE, Hernández-Blanco ML, et al. Thyroid hormones and breast cancer association according to menopausal status and body mass index. Breast cancer research : BCR. 2018;20(1):94.

69. Yuan S, Kar S, Vithayathil M, Carter P, Mason AM, Burgess S, et al. Causal associations of thyroid function and dysfunction with overall, breast and thyroid cancer: A two-sample Mendelian randomization study. International journal of cancer. 2020.

70. Fang Y, Yao L, Sun J, Yang R, Chen Y, Tian J, et al. Does thyroid dysfunction increase the risk of breast cancer? A systematic review and meta-analysis. Journal of endocrinological investigation. 2017;40(10):1035-47.

71. Angelousi AG, Anagnostou VK, Stamatakos MK, Georgiopoulos GA, Kontzoglou KC. Primary HT and risk for breast cancer: a systematic review and meta-analysis. European journal of endocrinology. 2012;166(3):373-81.

72. Hardefeldt PJ, Eslick GD, Edirimanne S. Benign thyroid disease is associated with breast cancer: a meta-analysis. Breast cancer research and treatment. 2012;133(3):1169-77.

73. Sarlis NJ, Gourgiotis L, Pucino F, Tolis GJ. Lack of association between Hashimoto thyroiditis and breast cancer: a quantitative research synthesis. HORMONES-ATHENS-. 2002;1:35-41.

74. Weng CH, Okawa ER, Roberts MB, Park SK, Umbricht CB, Manson JE, et al. Breast Cancer Risk in Postmenopausal Women with Medical History of Thyroid Disorder in the Women's Health Initiative. Thyroid : official journal of the American Thyroid Association. 2020;30(4):519-30.

75. Søgaard M, Farkas DK, Ehrenstein V, Jørgensen JO, Dekkers OM, Sørensen HT. Hypothyroidism and hyperthyroidism and breast cancer risk: a nationwide cohort study. European journal of endocrinology. 2016;174(4):409-14.

76. Yang H, Holowko N, Grassmann F, Eriksson M, Hall P, Czene K. Hyperthyroidism is associated with breast cancer risk and mammographic and genetic risk predictors. BMC medicine. 2020;18(1):225-.

77. Metso S, Auvinen A, Huhtala H, Salmi J, Oksala H, Jaatinen P. Increased cancer incidence after radioiodine treatment for hyperthyroidism. Cancer. 2007;109(10):1972-9.

78. Chen YK, Lin CL, Chang YJ, Cheng FT, Peng CL, Sung FC, et al. Cancer risk in patients with Graves' disease: a nationwide cohort study. Thyroid : official journal of the American Thyroid Association. 2013;23(7):879-84.

79. Brandt F, Thvilum M, Almind D, Christensen K, Green A, Hegedüs L, et al. Morbidity before and after the diagnosis of hyperthyroidism: a nationwide register-based study. PloS one. 2013;8(6):e66711.

80. Chaker L, Ligthart S, Korevaar TI, Hofman A, Franco OH, Peeters RP, et al. Thyroid function and risk of type 2 diabetes: a population-based prospective cohort study. BMC medicine. 2016;14(1):150.

81. Berta E, Lengyel I, Halmi S, Zrínyi M, Erdei A, Harangi M, et al. Hypertension in Thyroid Disorders. Frontiers in endocrinology. 2019;10:482.

82. Danzi S, Klein I. Thyroid hormone and blood pressure regulation. Current hypertension reports. 2003;5(6):513-20.

83. Siegmann EM, Müller HHO, Luecke C, Philipsen A, Kornhuber J, Grömer TW. Association of Depression and Anxiety Disorders With Autoimmune Thyroiditis: A Systematic Review and Meta-analysis. JAMA psychiatry. 2018;75(6):577-84.

84. Allen N, Sudlow C, Downey P, Peakman T, Danesh J, Elliott P, et al. UK Biobank: Current status and what it means for epidemiology. Health Policy and Technology. 2012;1(3):123-6.

85. Fry A, Littlejohns TJ, Sudlow C, Doherty N, Adamska L, Sprosen T, et al. Comparison of Sociodemographic and Health-Related Characteristics of UK Biobank Participants With Those of the General Population. American journal of epidemiology. 2017;186(9):1026-34.

86. Batty GD, Gale CR, Kivimäki M, Deary IJ, Bell S. Comparison of risk factor associations in UK Biobank against representative, general population based studies with conventional response rates: prospective cohort study and individual participant meta-analysis. BMJ. 2020;368:m131.

87. Sudlow C, Gallacher J, Allen N, Beral V, Burton P, Danesh J, et al. UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. PLoS medicine. 2015;12(3):e1001779.

88. UK Biobank. UK Biobank: Protocol for a large-scale prospective epidemiological resource 2007 [Available from: https://www.ukbiobank.ac.uk/media/gnkeyh2q/study-rationale.pdf.

89. Curado M-P, Edwards B, Shin HR, Storm H, Ferlay J, Heanue M, et al. Cancer incidence in five continents, Volume IX: IARC Press, International Agency for Research on Cancer; 2007.

90. Henson KE, Elliss-Brookes L, Coupland VH, Payne E, Vernon S, Rous B, et al. Data Resource Profile: National Cancer Registration Dataset in England. International journal of epidemiology. 2019;49(1):16-h.

91. Møller H, Richards S, Hanchett N, Riaz SP, Lüchtenborg M, Holmberg L, et al. Completeness of case ascertainment and survival time error in English cancer registries: impact on 1-year survival estimates. British journal of cancer. 2011;105(1):170-6.

92. Merriel SWD, Turner EL, Walsh E, Young GJ, Metcalfe C, Hounsome L, et al. Cross-sectional study evaluating data quality of the National Cancer Registration and Analysis Service (NCRAS) prostate cancer registry data using the Cluster randomised trial of PSA testing for Prostate cancer (CAP). BMJ open. 2017;7(11):e015994.

93. Woods LM, Coleman MP, Lawrence G, Rashbass J, Berrino F, Rachet B. Evidence against the proposition that "UK cancer survival statistics are misleading": simulation study with National Cancer Registry data. Bmj. 2011;342:d3399.

94. Office for National Statistics. Cancer registration statistics QMI [Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/methodologies/cancerregistrationstatisticsqmi.

95. Gastrell J, Griffiths C, Devis T. An analysis of legally uncertified deaths in England and Wales, 1979-2002. Health statistics quarterly. 2004(24):7-13.

96. Office for National Statistics. User guide to mortality statistics [Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/methodologies/userguidetomortalitystatisticsjuly2017.

97. Herbert A, Wijlaars L, Zylbersztejn A, Cromwell D, Hardelid P. Data Resource Profile: Hospital Episode Statistics Admitted Patient Care (HES APC). International journal of epidemiology. 2017;46(4):1093-i.

98. NHS information centre. The quality of nationally submitted health and social care data. England – First Annual Report, 2012, Experimental Statistics 2012 [Available from: https://digital.nhs.uk/data-and-information/publications/statistical/the-quality-of-nationally-submitted-health-and-social-care-data/the-quality-of-nationally-submitted-health-and-social-care-data-in-england-2012-first-annual-report-experimental-statistics.

99. Hall P, Holm LE, Lundell G, Bjelkengren G, Larsson LG, Lindberg S, et al. Cancer risks in thyroid cancer patients. British journal of cancer. 1991;64(1):159-63.

100. Dottorini ME, Lomuscio G, Mazzucchelli L, Vignati A, Colombo L. Assessment of female fertility and carcinogenesis after iodine-131 therapy for differentiated thyroid carcinoma. Journal of nuclear medicine : official publication, Society of Nuclear Medicine. 1995;36(1):21-7.

101. de Vathaire F, Schlumberger M, Delisle MJ, Francese C, Challeton C, de la Genardiére E, et al. Leukaemias and cancers following iodine-131 administration for thyroid cancer. British journal of cancer. 1997;75(5):734-9.

102. Rubino C, de Vathaire F, Dottorini ME, Hall P, Schvartz C, Couette JE, et al. Second primary malignancies in thyroid cancer patients. British journal of cancer. 2003;89(9):1638-44.

103. Bolch WE, Eckerman KF, Sgouros G, Thomas SR. MIRD pamphlet No. 21: a generalized schema for radiopharmaceutical dosimetry--standardization of nomenclature. Journal of nuclear medicine : official publication, Society of Nuclear Medicine. 2009;50(3):477-84.

104. Lamart S, Simon SL, Bouville A, Moroz BE, Lee C. S values for 131I based on the ICRP adult voxel phantoms. Radiat Prot Dosimetry. 2016;168(1):92-110.

105. Lamart S, Bouville A, Simon SL, Eckerman KF, Melo D, Lee C. Comparison of internal dosimetry factors for three classes of adult computational phantoms with emphasis on I-131 in the thyroid. Physics in medicine and biology. 2011;56(22):7317-35.

106. ICRP. Adult reference computational phantoms. Annals of the ICRP. 2009;39:1-166.

107. Remy H, Borget I, Leboulleux S, Guilabert N, Lavielle F, Garsi J, et al. 131I effective half-life and dosimetry in thyroid cancer patients. Journal of nuclear medicine : official publication, Society of Nuclear Medicine. 2008;49(9):1445-50.

108. Francois P, Beurtheret C, Dutreix A. Calculation of the dose delivered to organs outside the radiation beams. Medical physics. 1988;15(6):879-83.

109. Francois P, Beurtheret C, Dutreix A, De Vathaire F. A mathematical child phantom for the calculation of dose to the organs at risk. Medical physics. 1988;15(3):328-33.

110. Diallo I, Lamon A, Shamsaldin A, Grimaud E, de Vathaire F, Chavaudra J. Estimation of the radiation dose delivered to any point outside the target volume per patient treated with external beam radiotherapy. Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology. 1996;38(3):269-71.

111. Little RJ, Rubin DB. Statistical analysis with missing data: John Wiley & Sons; 2019.

112. Andridge RR, Little RJ. A Review of Hot Deck Imputation for Survey Non-response. International statistical review = Revue internationale de statistique. 2010;78(1):40-64.

113. Cox DR. Regression Models and Life-Tables. Journal of the Royal Statistical Society Series B (Methodological). 1972;34(2):187-220.

114. Maldonado G, Greenland S. Simulation study of confounder-selection strategies. American journal of epidemiology. 1993;138(11):923-36.

115. Lau B, Cole SR, Gange SJ. Competing Risk Regression Models for Epidemiologic Data. American journal of epidemiology. 2009;170(2):244-56.

116. Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al. Cochrane handbook for systematic reviews of interventions: John Wiley & Sons; 2019.

117. Sacks HS, Berrier J, Reitman D, Ancona-Berk V, Chalmers TC. Meta-analyses of randomized controlled trials. New England Journal of Medicine. 1987;316(8):450-5.

118. Viechtbauer W, Cheung MW. Outlier and influence diagnostics for meta-analysis. Research synthesis methods. 2010;1(2):112-25.

119. Rothstein HR, Sutton AJ, Borenstein M. Publication bias in meta-analysis. Publication bias in meta-analysis: Prevention, assessment and adjustments. 2005:1-7.

120. Breslow NE, Day NE. Statistical Methods in Cancer Research, Volume 2: The Design and Analysis of Cohort Studies. Lyon: International agency for research on cancer. 1987.

121. VanderWeele TJ. Mediation Analysis: A Practitioner's Guide. Annual review of public health. 2016;37:17-32.

122. Richiardi L, Bellocco R, Zugna D. Mediation analysis in epidemiology: methods, interpretation and bias. International journal of epidemiology. 2013;42(5):1511-9.

123. Nguyen TQ, Schmid I, Stuart EA. Clarifying causal mediation analysis for the applied researcher: Defining effects based on what we want to learn. Psychological methods. 2020.

124. Vansteelandt S, Daniel RM. Interventional Effects for Mediation Analysis with Multiple Mediators. Epidemiology (Cambridge, Mass). 2017;28(2):258-65.

125. Hernán MA, Robins JM. Causal inference. CRC Boca Raton, FL;; 2010.

126. Cole SR, Frangakis CE. The consistency statement in causal inference: a definition or an assumption? Epidemiology (Cambridge, Mass). 2009;20(1):3-5.

127. Westreich D, Cole SR. Invited commentary: positivity in practice. American journal of epidemiology. 2010;171(6):674-7.

128. Hernán MA. Beyond exchangeability: the other conditions for causal inference in medical research. Sage Publications Sage UK: London, England; 2012.

129. Robins J. A new approach to causal inference in mortality studies with a sustained exposure period—application to control of the healthy worker survivor effect. Mathematical Modelling. 1986;7(9):1393-512.

130. Lin SH, Young JG, Logan R, VanderWeele TJ. Mediation analysis for a survival outcome with time-varying exposures, mediators, and confounders. Statistics in medicine. 2017;36(26):4153-66.

131. Wang A, Arah OA. G-computation demonstration in causal mediation analysis. Eur J Epidemiol. 2015;30(10):1119-27.

132. Taubman SL, Robins JM, Mittleman MA, Hernán MA. Intervening on risk factors for coronary heart disease: an application of the parametric g-formula. International journal of epidemiology. 2009;38(6):1599-611.

133. Tran TV, Maringe C, Benitez Majano S, Rachet B, Boutron-Ruault MC, Journy N. Thyroid dysfunction and breast cancer risk among women in the UK Biobank cohort. Cancer medicine. 2021;10(13):4604-14.

134. Eastwood SV, Mathur R, Atkinson M, Brophy S, Sudlow C, Flaig R, et al. Algorithms for the Capture and Adjudication of Prevalent and Incident Diabetes in UK Biobank. PLoS One. 2016;11(9):e0162388-e.

135. Schairer C, Pfeiffer RM, Gadalla SM. Autoimmune diseases and breast cancer risk by tumor hormone-receptor status among elderly women. International journal of cancer. 2018;142(6):1202-8.

136. Thomas SL, Griffiths C, Smeeth L, Rooney C, Hall AJ. Burden of mortality associated with autoimmune diseases among females in the United Kingdom. American journal of public health. 2010;100(11):2279-87.

137. Eaton WW, Pedersen MG, Atladóttir HO, Gregory PE, Rose NR, Mortensen PB. The prevalence of 30 ICD-10 autoimmune diseases in Denmark. Immunologic research. 2010;47(1-3):228-31.

138. Knol MJ, VanderWeele TJ. Recommendations for presenting analyses of effect modification and interaction. International journal of epidemiology. 2012;41(2):514-20.

139. Okosieme OE, Taylor PN, Evans C, Thayer D, Chai A, Khan I, et al. Primary therapy of Graves' disease and cardiovascular morbidity and mortality: a linked-record cohort study. The lancet Diabetes & endocrinology. 2019;7(4):278-87.

140. Putter H, Fiocco M, Geskus RB. Tutorial in biostatistics: competing risks and multi-state models. Statistics in medicine. 2007;26(11):2389-430.

141. Moher D, Liberati A, Tetzlaff J, Altman DG, Group atP. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA StatementThe PRISMA Statement. Annals of Internal Medicine. 2009;151(4):264-9.

142. Angelousi AG, Anagnostou VK, Stamatakos MK, Georgiopoulos GA, Kontzoglou KC. Mechanisms in endocrinology: primary HT and risk for breast cancer: a systematic review and meta-analysis. European journal of endocrinology. 2012;166(3):373-81.

143. Franceschi S, Preston-Martin S, Dal Maso L, Negri E, La Vecchia C, Mack WJ, et al. A pooled analysis of case–control studies of thyroid cancer. IV. Benign thyroid diseases. Cancer Causes & Control. 1999;10(6):583-95.

144. Sarlis NJ, Gourgiotis L, Pucino F, Tolis GJ. Lack of association between Hashimoto thyroiditis and breast cancer: a quantitative research synthesis. Hormones. 2002;1:35-41.

145. DerSimonian R, Laird N. Meta-analysis in clinical trials. Controlled clinical trials. 1986;7(3):177-88.

146. Petitti DB. Approaches to heterogeneity in meta-analysis. Statistics in medicine. 2001;20(23):3625-33.

147. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Statistics in medicine. 2002;21(11):1539-58.

148. Viechtbauer W, Cheung MWL. Outlier and influence diagnostics for meta-analysis. Res Synth Methods. 2010;1(2):112-25.

149. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. Bmj. 1997;315(7109):629-34.

150. Chan YX, Knuiman MW, Divitini ML, Brown SJ, Walsh J, Yeap BB. Lower TSH and higher free thyroxine predict incidence of prostate but not breast, colorectal or lung cancer. European journal of endocrinology. 2017;177(4):297-308.

151. Chen Y-K, Lin C-L, Chang Y-J, Cheng FT-F, Peng C-L, Sung F-C, et al. Cancer risk in patients with Graves' disease: a nationwide cohort study. Thyroid : official journal of the American Thyroid Association. 2013;23(7):879-84.

152. Chen Y, Lin C, Cheng FT, Sung F, Kao C. Cancer risk in patients with Hashimoto's thyroiditis: a nationwide cohort study. British journal of cancer. 2013;109(9):2496.

153. Hellevik AI, Åsvold BO, Bjøro T, Romundstad PR, Nilsen TIL, Vatten LJ. Thyroid function and cancer risk: a prospective population study. Cancer Epidemiology and Prevention Biomarkers. 2009;18(2):570-4.

154. Mellemgaard A, From G, Jørgensen T, Johansen C, Olsen JH, Perrild H. Cancer risk in individuals with benign thyroid disorders. Thyroid : official journal of the American Thyroid Association. 1998;8(9):751-4.

155. Metso S, Auvinen A, Huhtala H, Salmi J, Oksala H, Jaatinen P. Increased cancer incidence after radioiodine treatment for hyperthyroidism. Cancer: Interdisciplinary International Journal of the American Cancer Society. 2007;109(10):1972-9.

156. Cristofanilli M, Yamamura Y, Kau SW, Bevers T, Strom S, Patangan M, et al. Thyroid hormone and breast carcinoma: primary hypothyroidism is associated with a reduced incidence of primary breast carcinoma. Cancer: Interdisciplinary International Journal of the American Cancer Society. 2005;103(6):1122-8.

157. Goldman MB, Maloof F, Monson RR, Aschengrau A, Cooper DS, Ridgway EC. Radioactive iodine therapy and breast cancer: a follow-up study of hyperthyroid women. American journal of epidemiology. 1988;127(5):969-80.

158. Munoz JM, Gorman CA, Elveback LR, Wentz JR. Incidence of malignant neoplasms of all types in patients with Graves' disease. Archives of internal medicine. 1978;138(6):944-7.

159. Talamini R, Franceschi S, Favero A, Negri E, Parazzini F, La Vecchia C. Selected medical conditions and risk of breast cancer. British journal of cancer. 1997;75(11):1699.

160. Bach L, Kostev K, Schiffmann L, Kalder M. Association between thyroid gland diseases and breast cancer: a case-control study. Breast cancer research and treatment. 2020;182(1):207-13.

161. Cristofanilli M, Yamamura Y, Kau SW, Bevers T, Strom S, Patangan M, et al. Thyroid hormone and breast carcinoma. Primary hypothyroidism is associated with a reduced incidence of primary breast carcinoma. Cancer. 2005;103(6):1122-8.

162. Chen YK, Lin CL, Cheng FT, Sung FC, Kao CH. Cancer risk in patients with Hashimoto's thyroiditis: a nationwide cohort study. British journal of cancer. 2013;109(9):2496-501.

163. Goldman MB, Maloof F, Monson RR, Aschengrau A, Cooper DS, Ridgway EC. Radioactive iodine therapy and breast cancer. A follow-up study of hyperthyroid women. American journal of epidemiology. 1988;127(5):969-80.

164. Mellemgaard A, From G, Jørgensen T, Johansen C, Olsen JH, Perrild H. Cancer risk in individuals with benign thyroid disorders. Thyroid : official journal of the American Thyroid Association. 1998;8(9):751-4.

165. Kitahara CM, Berrington de Gonzalez A, Bouville A, Brill AB, Doody MM, Melo DR, et al. Association of Radioactive Iodine Treatment With Cancer Mortality in Patients With Hyperthyroidism. JAMA internal medicine. 2019;179(8):1034-42.

166. Kahaly GJ, Bartalena L, Hegedüs L, Leenhardt L, Poppe K, Pearce SH. 2018 European Thyroid Association Guideline for the Management of Graves' Hyperthyroidism. European thyroid journal. 2018;7(4):167-86.

167. De Leo S, Lee SY, Braverman LE. Hyperthyroidism. Lancet (London, England). 2016;388(10047):906-18.

168. Morris DH, Jones ME, Schoemaker MJ, Ashworth A, Swerdlow AJ. Familial concordance for age at natural menopause: results from the Breakthrough Generations Study. Menopause (New York, NY). 2011;18(9):956-61.

169. Murabito JM, Yang Q, Fox C, Wilson PW, Cupples LA. Heritability of age at natural menopause in the Framingham Heart Study. The Journal of clinical endocrinology and metabolism. 2005;90(6):3427-30.

170. Collaborative Group on Hormonal Factors in Breast Cancer. Menarche, menopause, and breast cancer risk: individual participant meta-analysis, including 118 964 women with breast cancer from 117 epidemiological studies. The Lancet Oncology. 2012;13(11):1141-51.

171. Cleary MP, Grossmann ME. Minireview: Obesity and breast cancer: the estrogen connection. Endocrinology. 2009;150(6):2537-42.

172. Tosovic A, Becker C, Bondeson AG, Bondeson L, Ericsson UB, Malm J, et al. Prospectively measured thyroid hormones and thyroid peroxidase antibodies in relation to breast cancer risk. International journal of cancer. 2012;131(9):2126-33.

173. Tosovic A, Bondeson A-G, Bondeson L, Ericsson U-B, Malm J, Manjer J. Prospectively measured triiodothyronine levels are positively associated with breast cancer risk in postmenopausal women. Breast Cancer Research. 2010;12(3):R33.

174. Council NR. Health risks from exposure to low levels of ionizing radiation: BEIR VII phase 2. 2006.

175. Preston DL, Mattsson A, Holmberg E, Shore R, Hildreth NG, Boice JD, Jr. Radiation effects on breast cancer risk: a pooled analysis of eight cohorts. Radiat Res. 2002;158(2):220-35.

176. Ronckers CM, Erdmann CA, Land CE. Radiation and breast cancer: a review of current evidence. Breast cancer research : BCR. 2005;7(1):21-32.

177. Land CE, Tokunaga M, Koyama K, Soda M, Preston DL, Nishimori I, et al. Incidence of female breast cancer among atomic bomb survivors, Hiroshima and Nagasaki, 1950-1990. Radiation research. 2003;160(6):707-17.

178. Ulm K. A statistical method for assessing a threshold in epidemiological studies. Statistics in medicine. 1991;10(3):341-9.

179. Berrington de Gonzalez A, Gilbert E, Curtis R, Inskip P, Kleinerman R, Morton L, et al. Second solid cancers after radiation therapy: a systematic review of the epidemiologic studies of the radiation dose-response relationship. Int J Radiat Oncol Biol Phys. 2013;86(2):224-33.

180. Preston DL, Kitahara CM, Freedman DM, Sigurdson AJ, Simon SL, Little MP, et al. Breast cancer risk and protracted low-to-moderate dose occupational radiation exposure in the US Radiologic Technologists Cohort, 1983-2008. British journal of cancer. 2016;115(9):1105-12.

181. Preston DL, Ron E, Tokuoka S, Funamoto S, Nishi N, Soda M, et al. Solid cancer incidence in atomic bomb survivors: 1958-1998. Radiat Res. 2007;168(1):1-64.

182. Brenner AV, Preston DL, Sakata R, Sugiyama H, de Gonzalez AB, French B, et al. Incidence of Breast Cancer in the Life Span Study of Atomic Bomb Survivors: 1958-2009. Radiat Res. 2018;190(4):433-44.

183. Davis FG, Yu KL, Preston D, Epifanova S, Degteva M, Akleyev AV. Solid Cancer Incidence in the Techa River Incidence Cohort: 1956-2007. Radiat Res. 2015;184(1):56-65.

184. Teng CJ, Hu YW, Chen SC, Yeh CM, Chiang HL, Chen TJ, et al. Use of Radioactive Iodine for Thyroid Cancer and Risk of Second Primary Malignancy: A Nationwide Population-Based Study. Journal of the National Cancer Institute. 2016;108(2).

185. Ahn HY, Min HS, Yeo Y, Ma SH, Hwang Y, An JH, et al. Radioactive Iodine Therapy Did Not Significantly Increase the Incidence and Recurrence of Subsequent Breast Cancer. The Journal of clinical endocrinology and metabolism. 2015;100(9):3486-93.

186. Lin CY, Lin CL, Huang WS, Kao CH. Risk of Breast Cancer in Patients with Thyroid Cancer Receiving or Not Receiving 131I Treatment: A Nationwide Population-Based Cohort Study. Journal of nuclear medicine : official publication, Society of Nuclear Medicine. 2016;57(5):685-90.

187. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, et al. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid. 2016;26(1):1-133.

188. Luster M, Clarke SE, Dietlein M, Lassmann M, Lind P, Oyen WJ, et al. Guidelines for radioiodine therapy of differentiated thyroid cancer. European journal of nuclear medicine and molecular imaging. 2008;35(10):1941-59.

189. Krashin E, Piekiełko-Witkowska A, Ellis M, Ashur-Fabian O. Thyroid Hormones and Cancer: A Comprehensive Review of Preclinical and Clinical Studies. Frontiers in endocrinology. 2019;10:59.

190. Tang HY, Lin HY, Zhang S, Davis FB, Davis PJ. Thyroid hormone causes mitogen-activated protein kinase-dependent phosphorylation of the nuclear estrogen receptor. Endocrinology. 2004;145(7):3265-72.

191. Hall LC, Salazar EP, Kane SR, Liu N. Effects of thyroid hormones on human breast cancer cell proliferation. The Journal of steroid biochemistry and molecular biology. 2008;109(1-2):57-66.

192. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. World Health Organization technical report series. 2000;894:i-xii, 1-253.

193. Fan M, Lyu J, He P. Guidelines for data processing and analysis of the International Physical Activity Questionnaire (IPAQ).2005. URL: <http://www.IPAQ.ki.se. Zhonghua liu xing bing xue za zhi = Zhonghua liuxingbingxue zazhi. 2014;35:961-4.

194. Shrier I, Platt RW. Reducing bias through directed acyclic graphs. BMC medical research methodology. 2008;8:70.

195. VanderWeele TJ, Shpitser I. A new criterion for confounder selection. Biometrics. 2011;67(4):1406-13.

196. Buchanan AL, Hudgens MG, Cole SR, Lau B, Adimora AA. Worth the weight: using inverse probability weighted Cox models in AIDS research. AIDS research and human retroviruses. 2014;30(12):1170-7.

197. Cole SR, Hernán MA. Constructing Inverse Probability Weights for Marginal Structural Models. American journal of epidemiology. 2008;168(6):656-64.

198. Howe CJ, Cole SR, Westreich DJ, Greenland S, Napravnik S, Eron JJ, Jr. Splines for trend analysis and continuous confounder control. Epidemiology (Cambridge, Mass). 2011;22(6):874-5.

199. Austin PC. Variance estimation when using inverse probability of treatment weighting (IPTW) with survival analysis. Statistics in medicine. 2016;35(30):5642-55.

200. Travis LB, Hill DA, Dores GM, Gospodarowicz M, van Leeuwen FE, Holowaty E, et al. Breast cancer following radiotherapy and chemotherapy among young women with Hodgkin disease. Jama. 2003;290(4):465-75.

201. Guibout C, Adjadj E, Rubino C, Shamsaldin A, Grimaud E, Hawkins M, et al. Malignant breast tumors after radiotherapy for a first cancer during childhood. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2005;23(1):197-204.

202. Inskip PD, Robison LL, Stovall M, Smith SA, Hammond S, Mertens AC, et al. Radiation dose and breast cancer risk in the childhood cancer survivor study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2009;27(24):3901-7.

PUBLICATIONS DURING THE THESIS

RESEARCH

Thyroid dysfunction and cancer incidence: a systematic review and meta-analysis

Thi-Van-Trinh Tran[1], Cari M Kitahara[2], Florent de Vathaire[1], Marie-Christine Boutron-Ruault[3] and **Neige Journy[1]**

[1]Cancer and Radiation Group, Center for Research in Epidemiology and Population Health, INSERM U1018, Paris Sud-Paris Saclay University, Gustave Roussy, Villejuif, France
[2]Radiation Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Bethesda, Maryland, USA
[3]Health Across Generations Group, Center for Research in Epidemiology and Population Health, INSERM U1018, Paris Sud-Paris Saclay University, Gustave Roussy, Villejuif, France

Correspondence should be addressed to T-V-T Tran: Thivantrinh.TRAN@gustaveroussy.fr

Abstract

In this study, we aimed to evaluate site-specific cancer risks associated with hyperthyroidism or hypothyroidism. We performed a systematic review of observational studies reporting associations between hyperthyroidism or hypothyroidism and subsequent site-specific cancer incidence, in MEDLINE and the COCHRANE library (inception-28/01/2019) (PROSPERO: CRD42019125094). We excluded studies with thyroid dysfunction evaluated as a cancer biomarker or after prior cancer diagnosis and those considering transient thyroid dysfunction during pregnancy or severe illnesses. Risk of bias was assessed using a modified Newcastle–Ottawa scale. Risk estimates were pooled using random-effects models when ≥5 studies reported data for a specific cancer site. Twenty studies were included, of which 15 contributed to the meta-analysis. Compared to euthyroidism, hyperthyroidism was associated with higher risks of thyroid (pooled risk ratio: 4.49, 95%CI: 2.84–7.12), breast (pooled risk ratio: 1.20, 95%CI: 1.04–1.38), and prostate (pooled risk ratio: 1.35, 95%CI: 1.05–1.74), but not respiratory tract (pooled risk ratio: 1.06, 95%CI: 0.80–1.42) cancers. Hypothyroidism was associated with a higher risk of thyroid cancer within the first 10 years of follow-up only (pooled risk ratio: 3.31, 95%CI: 1.20–9.13). There was no or limited evidence of thyroid dysfunction-related risks of other cancer sites. In conclusion, thyroid dysfunction was associated with increased risks of thyroid, breast, and prostate cancers. However, it remains unclear whether these findings represent causal relationships because information on treatments and potential confounders was frequently lacking.

Key Words

- hyperthyroidism
- hypothyroidism
- cancer
- incidence
- epidemiological studies
- meta-analysis

Endocrine-Related Cancer (2020) **27**, 245–259

Introduction

Thyroid dysfunction can present as decreased (hyperthyroidism) or elevated (hypothyroidism) thyroid-stimulating hormone (TSH) serum levels, leading to an increased or decreased production of thyroid hormones (triiodothyronine (T3) and/or thyroxin (T4)), respectively. Autoimmune conditions, such as Graves' disease (hyperthyroidism) and Hashimoto's thyroiditis (hypothyroidism), are the most common causes of thyroid dysfunction in iodine-replete areas. Thyroid dysfunction can occur in both sexes, but is particularly frequent

https://erc.bioscientifica.com
https://doi.org/10.1530/ERC-19-0417

among women aged 40 years and older, with a prevalence of 5–15% in iodine-replete communities (Garmendia Madariaga *et al.* 2014, Journy *et al.* 2017).

Thyroid dysfunction may be involved in carcinogenesis. Thyroid hormones and TSH can directly enhance tumor proliferation through their cell surface receptors, estrogen pathways, increased angiogenesis, and gene expression regulation (Moeller & Führer 2013, Hercbergs *et al.* 2018). Moreover, thyroid dysfunction is associated with obesity (Laurberg *et al.* 2012), diabetes mellitus (Brandt *et al.* 2013), and vascular diseases (Brandt *et al.* 2013), which have been linked to an increased cancer risk or shared common risk factors. However, epidemiological evidence on the association between thyroid dysfunction and cancer risk has been contradictory. Several studies have reported increased risks of thyroid or breast cancer associated with hyperthyroidism and decreased or unchanged risks with hypothyroidism, compared to euthyroid individuals (Cristofanilli *et al.* 2005, Balasubramaniam *et al.* 2012, Søgaard *et al.* 2016, Kitahara *et al.* 2018). However, in some other large cohorts, there was no association between thyroid dysfunction and cancer risk (Metso *et al.* 2007, Hellevik *et al.* 2009). Four previous meta-analyses on breast cancer found no significantly increased or decreased risks with thyroid dysfunction, but highlighted the heterogeneity of results across studies published from 2002 to 2016 (Sarlis *et al.* 2002, Angelousi *et al.* 2012, Hardefeldt *et al.* 2012, Fang *et al.* 2017). A pooled analysis of case-control studies published in 1984–1997 showed an increased risk of thyroid cancer with self-reported hyperthyroidism, but not with hypothyroidism (Franceschi *et al.* 1999). Interpretation of these results is nevertheless hampered by several factors: lack of longitudinal studies, lack of data on thyroid dysfunction treatments, inclusion of prevalent cancer cases, and the possibility of reverse causality. Recently, two additional large studies have provided new evidence of an elevated risk of thyroid cancer in relation to thyroid dysfunction (Huang *et al.* 2017, Kitahara *et al.* 2018). Other studies reported associations with other cancer sites, such as prostate and lung (Mellemgaard *et al.* 1998, Hellevik *et al.* 2009), which have not yet been analyzed in a systematic review or meta-analysis.

In this systematic review and meta-analysis, we comprehensively summarized the published evidence up to 2019 on the associations of hyperthyroidism and hypothyroidism with site-specific cancer incidence. We also reported the current evidence on cancer risks associated with thyroid dysfunction treatments.

Materials and methods

This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher *et al.* 2009) (Supplementary Appendix 1, see section on supplementary materials given at the end of this article). Our protocol was registered in the PROSPERO International prospective register of systematic reviews database (CRD42019125094) prior to study.

Search strategy

We performed a systematic literature search in PubMed/MEDLINE and the Cochrane library from inception to January 28, 2019. We included case-control and cohort studies that reported a measure of association between thyroid dysfunction (overt and subclinical) or thyroid hormone levels compatible with thyroid dysfunction diagnosed before cancer diagnosis (Box 1) and subsequent site-specific cancer risk. Our search strategy included MeSH terms and key words in the titles and abstracts (Supplementary Appendix 2). We restricted the search to English, French and Vietnamese languages, and to studies in humans. Reference lists of eligible articles and previous systematic reviews (Franceschi *et al.* 1999, Sarlis *et al.* 2002, Angelousi *et al.* 2012, Hardefeldt *et al.* 2012, Fang *et al.* 2017) were hand searched to identify additional relevant studies.

Study selection

One investigator (T V T T) screened the title and abstract of all articles identified in the initial search and reviewed

Box 1. Definition of hyperthyroidism and hypothyroidism used in the search.

- Overt or subclinical hyperthyroidism and hypothyroidism, reported in medical or laboratory records, questionnaires, registry or medico-administrative databases, or measured in blood samples, prior to cancer diagnosis. People with Graves' disease, toxic nodular goiter, and thyrotoxicosis were considered as hyperthyroid and those with Hashimoto's disease as hypothyroid.
- Thyroid-stimulating hormone (TSH), free thyroxine (FT4) and/or free triiodothyronine (FT3) levels beyond reference levels in iodine-replete populations: TSH 0.4–4.0 mIU/L, FT4 9–25 pmol/L (0.7–1.9 ng/dL), and FT3 3.5–7.8 nmol/L (0.2–0.5 ng/dL). When possible, overt and subclinical thyroid dysfunction was differentiated, as defined in Supplementary Appendix 5.

https://erc.bioscientifica.com
https://doi.org/10.1530/ERC-19-0417

the full text of potentially eligible articles. Our exclusion criteria were (1) hyperthyroidism and hypothyroidism not reported separately, (2) no information on specific cancer sites, (3) no reported measure of association between hyperthyroidism or hypothyroidism and cancer incidence, (4) thyroid dysfunction evaluated as a cancer biomarker (e.g. thyroid cancer), (5) thyroid dysfunction evaluated after cancer diagnosis or no/limited information on cancer history prior to thyroid dysfunction evaluation, (6) participants with a prior malignant condition or treated cancer, and (7) transient thyroid dysfunction during pregnancy or severe illnesses. Because thyroid dysfunction can also affect cancer survival (Sandhu *et al.* 2009, Minlikeeva *et al.* 2017), possibly through early or delayed cancer detection due to the management of thyroid function or associated comorbidities (e.g. diabetes, cardiovascular diseases) or differences in cancer treatment strategies due to the presence of comorbidities (Sarfati *et al.* 2016), it is difficult to disentangle the effects of thyroid dysfunction on cancer incidence and survival. Consequently, we disregarded studies on cancer mortality, of which only two (Goldman *et al.* 1988, Journy *et al.* 2017) excluded individuals with prior cancer history at thyroid dysfunction assessment (exclusion criterion #5; Fig. 1, Supplementary Appendix 6).

Data extraction

Using pre-defined data extraction forms, two investigators (T V T T and N J) independently extracted the following information from the included studies: study setting and design, sample size, follow-up methods and duration, participant characteristics (age, sex, and menopausal status), thyroid dysfunction (definition, ascertainment methods, and treatments), cancer outcomes (definition and ascertainment methods), methods for statistical analysis (risk modelling and adjustment variables), and multivariable analysis results, including cases, controls number, and risk estimates. We retrieved data from the most informative studies in case of duplicate data sources.

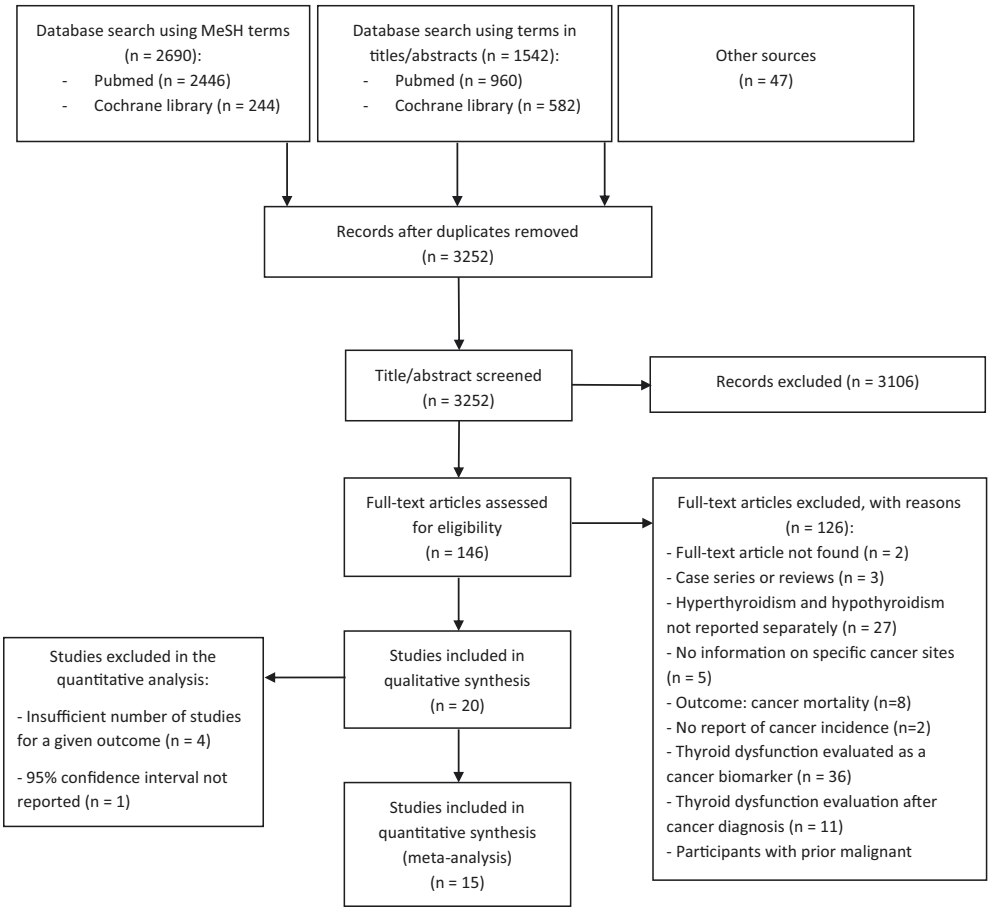


Figure 1
PRISMA flow diagram outlining search strategy and the final included and excluded studies.

https://erc.bioscientifica.com
https://doi.org/10.1530/ERC-19-0417

Previous reports of the study population were reviewed for additional information that was not available in the included article. Corresponding authors were contacted when necessary.

Quality assessment

Two investigators (T V T T and N J) independently assessed risk of bias of the included studies, in terms of participant selection, comparability of groups, and ascertainment of the outcome (in cohorts) or exposure (in case-control studies), using a modified Newcastle–Ottawa scale (NOS) (Wells 2001) (Supplementary Appendix 3). This scale contains a number of items (selection: $n=4$, comparability: $n=2$, outcome: $n=3$, and exposure: $n=5$), to which a point was awarded to modalities with the lowest risk of bias. To date, no consensus has been reached on the interpretation of assigned points to NOS items. Therefore, we arbitrarily considered ≥2, ≥1, ≥2, and ≥3 points as 'low-to-moderate' risk of bias for selection, comparability, outcome, and exposure domains, respectively (Supplementary Appendix 4). In studies investigating several outcomes, the risk of bias could vary according to the cancer of interest. Inconsistent ratings between the two investigators were resolved by discussion.

Statistical analysis

For each study, we extracted risk estimates (relative risk, odds ratio, hazard ratio, or standardized incidence ratio) adjusted for the most covariables and 95% CIs from the original article. We pooled risk ratios when associations of hyperthyroidism or hypothyroidism and site-specific cancer incidence were reported in five studies or more. Estimates for respiratory tract cancers were combined with those for lung cancer only, which accounts for more than 90% of the former category (Forman *et al.* 2013). Pooled risk ratios were estimated using DerSimonian and Laird random-effect models (DerSimonian & Laird 1986). In sensitivity analyses, we compared our results with those using fixed-effect models. For studies which reported only sex-specific risk ratios, these risk estimates were pooled using a fixed-effect model in order to have a single risk ratio per study.

Heterogeneity across studies was evaluated using the Q-statistic with a conservative 10% *P*-value because it has low power (Petitti 2001) and the I^2 statistic (Higgins & Thompson 2002), which represents the proportion of total variance of a pooled risk ratio attributable to variability across studies. An I^2 value greater than 50% indicates a substantial heterogeneity level. To explore the heterogeneity sources, we conducted analyses stratified by thyroid dysfunction treatments: no treatment, radioactive iodine (RAI) only, thyroid hormone replacement therapy (THRT) only, mixed modalities, or unspecified treatments. No studies have investigated surgery and anti-thyroid drugs as a unique treatment of thyroid dysfunction. Except for the study of Goldman *et al.* (1988) which had some follow-up data, we analyzed only treatments ascertained at study inclusion due to the unavailability of follow-up data in all other cohort studies. Furthermore, we estimated pooled risk ratios stratified by sex (men or women), methods for thyroid dysfunction ascertainment (in-/out-patient hospital diagnoses, or others), study design (cohort or case-control), and geographic region (Asia, Australia, Europe, or North America). We also used the Q-statistic to test for subgroup differences – with *P*-values <0.1 indicating evidence of heterogeneity. Other sensitivity analyses were restricted to studies with low-to-moderate risk of bias for each NOS domain or those with a minimum follow-up time of 1 year to minimize the probability of reverse causation (i.e. thyroid dysfunction due to cancer). We conducted an influence analysis by the leave-one-out method to assess whether the pooled risk estimates were driven by specific studies (Viechtbauer & Cheung 2010).

To further explore the possibility of reverse causation, we estimated pooled risk ratios as a function of time, since thyroid dysfunction diagnosis/detection in a meta-regression analysis (Thompson & Higgins 2002), among studies reporting risk ratios for at least two follow-up time categories. Only studies on thyroid cancer risk fulfilled this requirement. For each category, follow-up time was assigned as the midpoint between the upper and the lower bound. For open-ended upper categories, we applied the range of the previous category. We modeled the log (risk ratio) as a linear or non-linear function of follow-up time. Departure from linearity was assessed by testing the statistical significance of second and third degree polynomials terms and restricted cubic splines with four knots at 0.05, 0.35, 0.65, and 0.95 percentiles.

Publication bias was assessed by Egger tests and funnel plots (Egger *et al.* 1997). The analyses were performed in R version 3.5.3 (https://www.R-project.org/) using the 'meta' and 'metafor' packages.

Results

After screening the title and abstract of 3252 non-duplicated articles and reviewing the full text of

https://erc.bioscientifica.com
https://doi.org/10.1530/ERC-19-0417

146 potentially eligible articles, we included 20 studies (12 cohort and 8 case-control studies) in the literature synthesis (Fig. 1). Of these, 15 studies contributed to the meta-analysis for thyroid ($n=8$), breast ($n=9$), prostate ($n=6$), and respiratory tract ($n=7$) cancers.

Study characteristics

Studies were conducted in Europe ($n=6$), the USA ($n=9$), Taiwan ($n=3$), Kuwait ($n=1$), and Australia ($n=1$). Thirteen studies were population-based (Mellemgaard *et al.* 1998, Memon *et al.* 2002, Welzel *et al.* 2007, Hellevik *et al.* 2009, Balasubramaniam *et al.* 2012, Chen *et al.* 2013*a*,*b*, Kang *et al.* 2013, Yeh *et al.* 2013, Chan *et al.* 2017, Huang *et al.* 2017, Petrick *et al.* 2017, Kitahara *et al.* 2018), of which five were nationwide (Mellemgaard *et al.* 1998, Chen *et al.* 2013*a*,*b*, Kitahara *et al.* 2018) or nationally representative (Yeh *et al.* 2013), where thyroid dysfunction was assessed through in- and/or out-patient hospital databases (Table 1). Three population-based studies had information on serum TSH and/or thyroid hormones concentrations (Hassan *et al.* 2009, Hellevik *et al.* 2009, Chan *et al.* 2017). Differences in study design resulted in widely variable sample size (ranging from 342 to 4.5 million) and mean/median follow-up time (ranging from 6 to 17 years on average; not reported for 13 studies). Fourteen studies included both females (proportion: 39% to 90%) and males. In cohort studies, the prevalence of hyperthyroidism and hypothyroidism ranged respectively from 0.3% to 2.5% and 0.6% to 7.8% across cohorts, respectively (mean age at thyroid dysfunction assessment: 40 to 62 years). Treatment modalities of thyroid dysfunction were: RAI only (Metso *et al.* 2007), THRT only (Cristofanilli *et al.* 2005), mixed modalities (Munoz *et al.* 1978, Goldman *et al.* 1988, Kang *et al.* 2013), no treatment (Hellevik *et al.* 2009, Yeh *et al.* 2013, Chan *et al.* 2017), or unspecified (Talamini *et al.* 1997, Mellemgaard *et al.* 1998, Memon *et al.* 2002, Welzel *et al.* 2007, Hassan *et al.* 2009, Balasubramaniam *et al.* 2012, Mondul *et al.* 2012, Chen *et al.* 2013*a*,*b*, Huang *et al.* 2017, Petrick *et al.* 2017, Kitahara *et al.* 2018). Treatments were ascertained at study inclusion, since there was incomplete (Goldman *et al.* 1988) or no follow-up data in the original studies. Diabetes and overweight/obesity were the most commonly reported comorbidities, with a prevalence of 2–10% in cohorts and 10–46% in case-control studies. Overall, nine (45%) studies were considered as moderate-to-low risk of bias (Supplementary Appendix 4). Neither the funnel plots nor the Egger's test showed evidence of publication bias for any outcome (Supplementary Figs 1, 2, 3, 4, 5 and 6).

Thyroid cancer

Seven (Memon *et al.* 2002, Metso *et al.* 2007, Yeh *et al.* 2013, Balasubramaniam *et al.* 2012, Chen *et al.* 2013*a*, Huang *et al.* 2017, Kitahara *et al.* 2018) and five (Memon *et al.* 2002, Balasubramaniam *et al.* 2012, Chen *et al.* 2013*b*, Huang *et al.* 2017, Kitahara *et al.* 2018) studies reported risks associated with hyperthyroidism and hypothyroidism, respectively, with a total sample size of 12.9 million individuals. They consistently reported increased risks for both hyperthyroidism and hypothyroidism, reaching statistical significance in studies with the largest numbers of cases (Figs 2 and 3). Most studies regarding hyperthyroidism (Memon *et al.* 2002, Chen *et al.* 2013*a*, Yeh *et al.* 2013, Huang *et al.* 2017, Kitahara *et al.* 2018) and hypothyroidism (Memon *et al.* 2002, Chen *et al.* 2013*b*, Huang *et al.* 2017, Kitahara *et al.* 2018) had low-to-moderate risks of bias for the selection and outcome/exposure domains, but adjustment for potential confounding factors, particularly calendar year, BMI, diabetes, and reproductive factors, was lacking in some studies (Memon *et al.* 2002, Metso *et al.* 2007, Chen *et al.* 2013*a*,*b*). The pooled risk ratio was 4.49 (95%CI 2.83 to 7.12, 280 cases among the exposed) for hyperthyroidism and 3.31 (95%CI 1.20 to 9.13, 171 cases among the exposed) for hypothyroidism. However, there was a substantial evidence for heterogeneity in both analyses ($I^2>80\%$, $P<0.01$), due to different magnitudes of risk across studies. The log risk ratios of thyroid cancer linearly decreased with time since diagnosis/detection of hyperthyroidism (Balasubramaniam *et al.* 2012, Chen *et al.* 2013*a*, Yeh *et al.* 2013, Huang *et al.* 2017, Kitahara *et al.* 2018) and hypothyroidism (Balasubramaniam *et al.* 2012, Chen *et al.* 2013*b*, Huang *et al.* 2017, Kitahara *et al.* 2018) (Fig. 4). After 10 years of follow-up, the risk was no longer significantly increased in hypothyroid individuals (risk ratio=0.91, 95%CI 0.26 to 3.23, $I^2=87\%$, $P<0.0001$), but remained elevated in hyperthyroid individuals (risk ratio=2.50, 95%CI: 1.66 to 3.78, $I^2=47\%$, $P=0.02$). The detected outliers may indicate an under-estimation of the CI's upper bound, but the trend over time was consistent across studies.

There was a higher risk ratio for hyperthyroidism among untreated individuals (risk ratio=6.80, 95%CI 3.58 to 12.91) (Yeh *et al.* 2013) than among those treated with RAI only (risk ratio=1.80, 95%CI: 0.43 to 7.53) (Metso *et al.* 2007), though the difference among different treatment subgroups was not statistically significant ($p_{heterogeneity}=0.22$, Supplementary Fig. 8). However, very few studies enabled analyses stratified

https://erc.bioscientifica.com
https://doi.org/10.1530/ERC-19-0417

https://erc.bioscientifica.com
https://doi.org/10.1530/ERC-19-0417

Table 1 Characteristics of the 20 included studies.

Reference	Country	Study design	Methods of follow-up and cancer ascertainment	Follow-up time in years: mean/median (min-max)[a]	Size of study population	Age in years: mean/median (min-max)	% Women	% Post-menopausal (women)	Thyroid dysfunction			Statistical analysis	Covariates in multivariate analysis[b]
									Definition	Method of ascertainement	Treatment(s) (%)		
Munoz *et al.* (1978)	USA	Hospital-based cohort	Hospital medical records (2 centers)	13.8/NR (0.1-nr)	*n* = 342	NR	80.7	NR	Hyperthyroidism: Graves' disease	Medical/laboratory reports	Desiccated thyroid, levothyroxine, thyroidectomy, radioactive iodine, Lugol's iodine, antithyroid drugs	SIR	Age, sex
Goldman *et al.* (1988)	USA	Single-institution, hospital-based cohort	Cooperative Thyrotoxicosis Therapy Follow-up Study, hospital medical records, administrative databases (vital status), self-reported questionnaire	17/NR (1–33)	1762	47/NR (nr-nr)	100.0	NR	Treated hyperthyroidism	Hospital medical records, self-reported questionnaire, physical exams	Radioactive iodine (*n* = 1406), surgery (*n* = 573), antithyroid drugs (*n* = 1069) - combinations of these treatments were possible	SMR, SIR	Mortality analysis: age, calendar time Incidence analysis: age, calendar time, race
Mellemgaard *et al.* (1998)	Denmark	National cohort	National civil registration system, national cancer registry	NR/NR (1–15)	*n* = nr	NR/NR (0–100+) (64% > 50 years of age)	84.4[j]	NR	Hyperthyroidism: thyrotoxicosis (ICD-8-CM code: 242)	National insurance database: in-patient claims	NR	SIR	Age, sex, calendar time
Metso *et al.* (2007)	Finland	Hospital-based cohort	National population registry, national cancer registry	10/NR (0.1–39)	*n* = 5586	NR/62 (IQR 50–75)	83.6	NR	Hyperthyroidism treated with RAI (Graves' disease: 57%, toxic multinodular goiter or adenoma, 43%)	Hospital medical records	Radioactive iodine (100%), mean cumulative dose = 305 MBq (range: 55–2664 MBq)	Mantel-Haenszel's incidence rate ratios	Age, sex
Hellevik *et al.* (2009)	Norway	Population-based cohort	National cancer registry	NR/9 (0–10)	26,691	NR/NR (20-nr)	66.4	NR	Hyperthyroidism[c]: TSH < 0.50 mU/L; Hypothyroidism[c]: TSH≥3.6 mU/L; No self-reported thyroid disease (types: nr)	Baseline blood test (DEFLFIA from Wallac Oy[d])	None at baseline	Cox proportional hazards regression model	Age, sex, smoking status
Balasubramanian *et al.* (2012)	USA	Population-based cohort	Inpatient discharge records of US Veterans Affairs medical system	All: 11.7/NR (1–27) Cases: 7.3/NR (nr-nr)	4,501,578	NR/52.5 (18–100)	0.0	0.0	Hyperthyroidism: thyrotoxicosis (ICD-9-CM code: 242); Hypothyroidism: ICD-9-CM code: 244	Inpatient discharge records of US Veterans Affairs medical system	NR	Time-dependent Poisson regression model	Age, calendar time, race, follow-up time, number of hospitalizations
Yeh *et al.* (2013)	Taiwan	National-representative cohort	National insurance database (histological confirmation)	NR/NR (0.25–4)	*n* = 51,099	NR/NR (0–100+) (92% < 65 years old)	77.7	NR	Hyperthyroidism: ICD-9-CM code: 242	National insurance database: in- and out-patient claims	No radioactive iodine or thyroidectomy at baseline	Cox proportional hazards regression model	Age, sex, time, diabetes, hypertension, hyperlipidemia, gout, geographic region, income
Kang *et al.* (2013)	USA	Population-based cohort	Self-reported questionnaire, national death registry, US postal service	NR/6–8 (0–34)	EC analysis: *n* = 200,162[e] OC analysis: *n* = 217,342[e]	50/NR (25–100+)	100.0	NR	Hyperthyroidism/Graves' disease, Hypothyroidism	Baseline and follow-up self-reported questionnaires	Thyroid hormone replacement (levothyroxine), radioactive iodine, surgery, antithyroid drugs[i]	Cox proportional hazards regression model	Shared covariates: age, time, cohort (NHS/NHSII), BMI, parity, oral contraceptive use history, age at menarche, age at menopause, use of estrogen only postmenopausal hormone therapies, use of estrogen plus progestin only postmenopausal hormone therapy, use of other postmenopausal hormone therapy, infertility EC: ~ and cigarette smoking, family history of uterin cancer, diabetes, age at the last birth OC: ~ and family history of breast or ovarian cancer, hysterectomy, tubal ligation
Chen *et al.* (2013*a*)	Taiwan	National cohort	National insurance database (histological confirmation)	NR/NR (0–14)	25,125	42/NR (20–100+)	77.3	NR	Hyperthyroidism: Graves' disease (ICD-9-CM code: 242.0)	National insurance database: ≥3 in- and out-patient claims	Thyroidectomy (0,14%)[i]	Poisson regression model, Cox proportional hazards regression model	Age, sex, diabetes, hypertension, hyperlipidemia
Chen *et al.* (2013*b*)	Taiwan	National cohort	National insurance database (histological confirmation)	NR/NR (0–13)	7605	40/NR (0–100+)	90.1	NR	Hypothyroidism: Hashimoto's thyroiditis (ICD-9-CM code: 245.2)	National insurance database: in- and out-patient claims	NR	Poisson regression model, Cox proportional hazards regression model	Age, sex, diabetes, hypertension, hyperlipidemia, heart disease
Chan *et al.* (2017)	Australia	Population-based cohort	Regional cancer and death registries	NR/NR (2–20)	3649	51/NR (25–84)	55.5	52.1	Subclinical hyperthyroidism[c]: TSH < 0,4 mU/L and FT4 < 21.2 pmol/L; Subclinical hypothyroidism[c]: TSH > 4 mU/L and FT4 > 12.6 pmol/L	Baseline blood test (third generation assay)	No thyroid-related medications at baseline (thyroxine supplementation, anti-thyroid medications, lithium, amiodarone, carbamazepine or phenytoin use)	Cox proportional hazards regression model	Age, sex, marital status, occupation, smoking, alcohol consumption, physical activities, BMI, diabetes, menopausal status, oral contraceptive use or HRT use

Kitahara *et al.* (2018)	Denmark	National cohort	National civil registration system, national cancer registry	NR/8 (1–36)	*n* = 8,258,807	NR/58 (0–100+)	84.0	NR	Hyperthyroidism: ICD-8-CM code: 242 or ICD-10-CM code: E05; Hypothyroidism: ICD-8-CM code: 244 or ICD-10-CM codes: E02, E03.2–E03.9, E89.0	National insurance database: in-, out-patient and emergency claims	NR	SIR	Age, sex, calendar time
Talamini *et al.* (1997)	Italy	Hospital-based case-control	Hospital records (histological confirmation)	NR/NR (0-nr)	*n* = 5157	NR/56 (20–74)	100.0	64.5	Hyperthyroidism, hypothyroidism	Structured interview (wihin the year after cancer diagnosis)	NR	Logistic regression models	Age, study area, education, parity, BMI quintiles, menopausal status
Memon *et al.* (2002)	Kuwait	Population-based case-control	National cancer registry	NR/NR (3-nr)	*n* = 626	37/37 (6–69)[f]	76.0	NR	Hyperthyroidism, hypothyroidism	Interview (not blinded to case/control status)	NR	Conditional logistic regression model	Year of birth, sex, nationality, district of residence
Cristofanilli *et al.* (2005)	USA	Cancer screening center-based case-control	Hospital records (1 center)	NR/NR (0-nr)	*n* = 2224	51/NR (nr-nr)	100.0	63.7	Treated primary hypothyroidism	Self-reported questionnaire (blinded to case/control status)	Thyroid hormone replacement, e.g. Levothyroxine (100%)	Unconditional logistic regression model	Age, first degree family history of breast cancer, history of pregnancy, use of HRT, menopausal status
Welzel *et al.* (2007)	USA	Population-based case-control	National insurance database: ≥3-year in- and out-patient, skilled-nursing facility, hospice claims; multi-regional cancer registry	NR/NR (3-nr)[g]	ICC analysis: *n* = 103,317 ICC analysis: *n* = 103,331	77/NR (68–100+)[f]	63.7	NR	Hyperthyroidism: thyrotoxicosis (ICD-9-CM codes: 242.0)	National insurance database: ≥3-year in- and out-patient, skilled-nursing facility, hospice claims	NR	Logistic regression models	Age, sex, race, geographic region, low socioeconomic status-proxy
Hassan *et al.* (2009)	USA	Hospital-based case-control	Hospital records (1 center), pathology report	NR/NR (0-nr)	*n* = 1524	60-63/NR (nr-nr)	38.6	NR	Hyperthyroidism, hypothyroidism	Interview (not blinded to case/control status)	NR	Unconditional logistic regression model	Age, sex, race, educational level, smoking, alcohol consumption, diabetes, family history of cancer, and HBV/HCV infection
Mondul *et al.* (2012)	Finland	Case-control (follow-up a primary prevention randomized controlled trial)	National cancer registry, medical records, national registry of death causes	NR/NR (3–20)	*n* = 1201	NR/NR (53–90)	0.0	0.0	Hyperthyroidism[c]: TSH < 0.3 mU/L and TT4 > 12 mg/dL; Hypothyroidism[c]: TSH > 3.0 mU/L and TT4 < 4.6 mg/dL	Baseline blood test (Immulite 2500 immunoassay system[h])	NR	Conditional logistic regression model	Age, time since exposure ascertainment, BMI, serum concentrations of retinol, total cholesterol, alpha tocopherol, beta carotene, cigarettes smoked per day, years smoked, family history of prostate cancer, leisure time physical activity, education, marital status, urban residence, total intake of energy, dietary vitamin D, fruit, vegetables, red meat, alcohol, use of calcium supplements
Huang *et al.* (2017)	USA	Population-based case control	U.S. Department of defense cancer registry (histological confirmation)	NR/NR (0.2–12)	*n* = 1482	NR/NR (21–100+) (30% > 40 years of age)	46.0	NR	Hyperthyroidism[c]: TSH < 0.3 mU/L; Hypothyroidism[c]: TSH > 4.2 mU/L	Blood tests (Roche Cobas E601[h]), samples routinely collected and stored at the U.S. Department of Defense Serum Repository	NR	Conditional logistic regression model	Date of birth, sex, race/ethnicity, follow-up time, BMI, branch of military service
Petrick *et al.* (2017)	USA	Population-based case-control	National insurance database: ≥3-year in- and out-patient, skilled-nursing facility, hospice claims; multi-regional cancer registry	NR/NR (3-nr)[g]	ICC analysis: *n* = 325,707 ECC analysis: *n* = 326,596	77/NR (68–100+)[f]	61.5	NR	Hyperthyroidism: thyrotoxicosis (ICD-9-CM codes: 242.40, 242.41, 242.80, 242.81, 242.90, 242.91)	National insurance database: ≥3-year in- and out-patient, skilled-nursing facility, hospice claims	NR	Logistic regression models	Age, sex, race, geographic region, low socioeconomic status-proxy

[a]Until otherwise specified, follow-up time was determined as following: for cohort studies, the time on study, considered from the date of the thyroid dysfunction evaluation to the date of cancer diagnosis or end of follow-up; for case-control studies, the period when participants were diagnosed with thyroid dysfunction in the past before cancer diagnosis; [b]for main analysis; [c]TSH reference range in the analysis: Chan *et al.* (2017), 0.4–4.0 mU/L; Hellevik *et al.* (2009), 0.5–1.4 mU/L; Huang *et al.* (2017), 1.2–1.93 mU/L; Mondul *et al.* (2012), 0.3–3 mU/L; [d]DELFIA hTSH Ultra: sensitivity, 0.03 mU/L; and total analytic variation, <5%; [e]Number reported in the analysis was 177,848; [f]Mean age weighted based on the available study data; [g]Follow-up time since thyroid dysfunction evaluation to cancer diagnosis was 0 year; [h]Sensitivity, variation, and assay generation are not reported; [i]Not used in the analyses; [j]among exposed patients.

EC: endometrial cancer; ECC: extrahepatic cholangiocarcinoma; HRT: hormone replacement therapy; ICC: intrahepatic cholangiocarcinoma; NR: not reported; OC: ovarian cancer; SIR: standardized incidence ratio; SMR: standardized mortality ratio.

https://erc.bioscientifica.com
https://doi.org/10.1530/ERC-19-0417

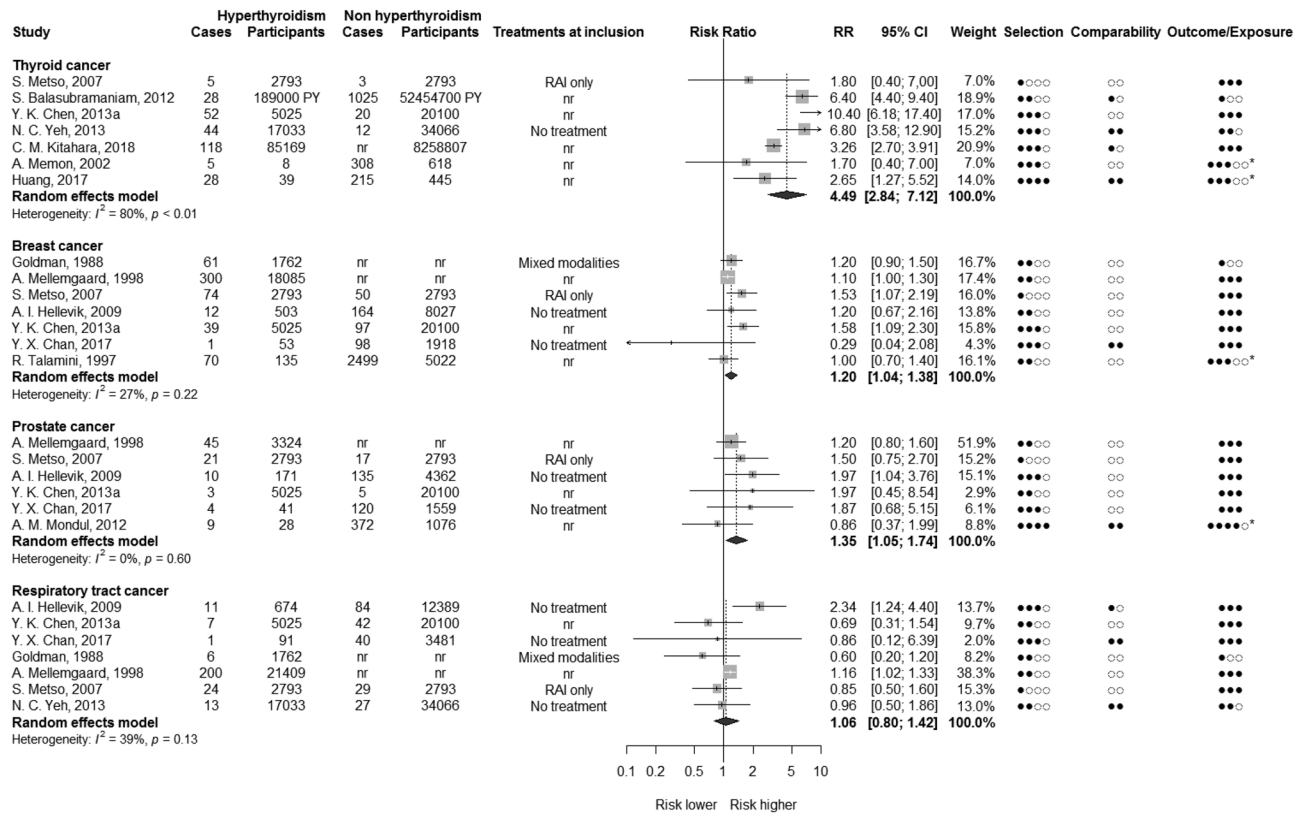


Figure 2
Forest plots for hyperthyroidism and the risk of different cancer sites and individual study risk of bias: overall risk ratios are displayed as diamonds. The size of each square is proportional to the weight of the study. CI: confidence interval; nr: not reported; PY: person-year; RAI: radioactive iodine; RR: risk ratio. *Case-control studies. Metso *et al*. (2007): results estimated based on a figure reporting the primary results of the article, exact results were not available. Mellemgaard *et al*. (1998): results for respiratory tract cancer pooled from separate risks for men and women reported with a fixed-effect model. Yeh *et al*. (2013) did not adjust for smoking but did adjust for all other important factors.

by treatment modalities for hyperthyroidism and none for hypothyroidism. Men with hyperthyroidism (risk ratio = 5.12, 95%CI 3.03 to 8.67) or hypothyroidism (risk ratio = 3.70, 95%CI 1.13 to 12.17) had higher risks than women with the same condition (hyperthyroidism: risk ratio = 3.87, 95%CI: 2.44 to 6.14; hypothyroidism: risk ratio = 1.30, 95%CI: 0.91 to 1.87), but the difference between sexes was not statistically significant

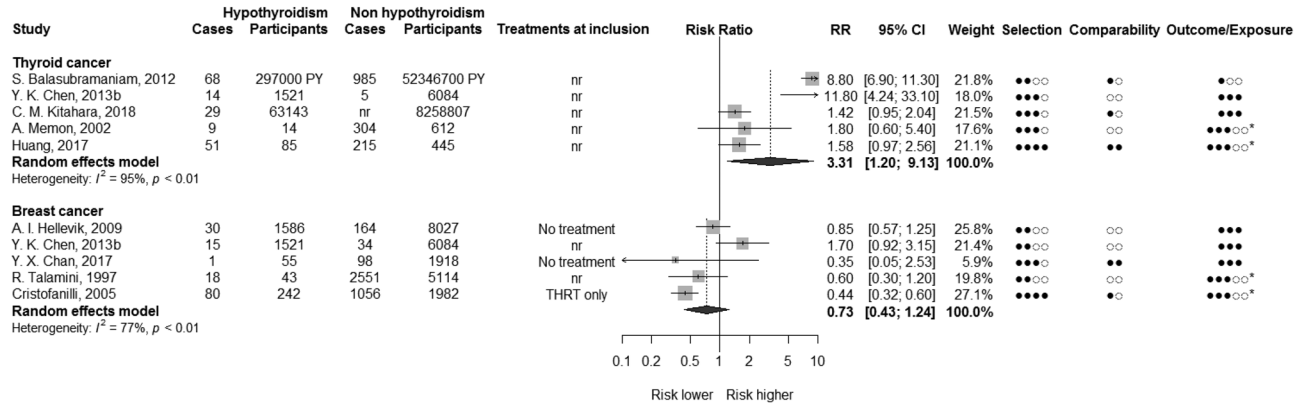


Figure 3
Forest plots for hypothyroidism and the risk of different cancer sites and individual study risk of bias: overall risk ratios are displayed as diamonds. The size of each square is proportional to the weight of the study. CI: confidence interval; nr: not reported; PY: person-year; RR: risk ratio; THRT: thyroid hormone replacement therapy. *Case-control studies.

https://erc.bioscientifica.com
https://doi.org/10.1530/ERC-19-0417

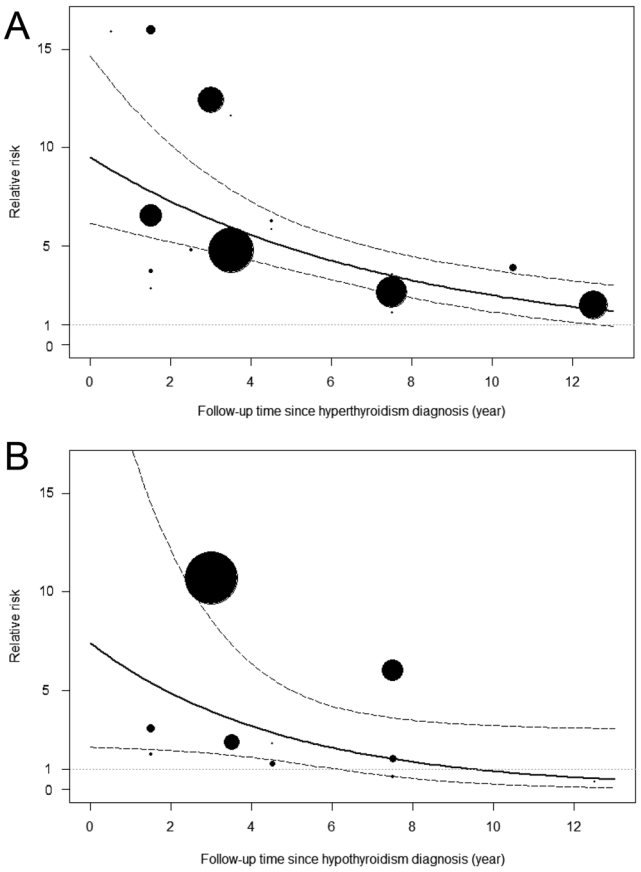


Figure 4
Effect of follow-up time on thyroid cancer risk of participants with thyroid dysfunction compared to euthyroid individuals. (A) For hyperthyroidism analysis. (B) For hypothyroidism analysis. Solid line: relative risk of thyroid cancer; dashed line: 95% confidence interval.

($p_{heterogeneity\ hyperthyroidism}$=0.43, $p_{heterogeneity\ hypothyroidism}$=0.10) (Supplementary Fig. 7). Moreover, for hypothyroidism, the subgroup analysis by sex was entirely driven by one study including only men that did not allow a comparison with women (Balasubramaniam *et al.* 2012).

Breast cancer

Risk of breast cancer associated with hyperthyroidism or hypothyroidism was investigated in seven (Goldman *et al.* 1988, Talamini *et al.* 1997, Mellemgaard *et al.* 1998, Metso *et al.* 2007, Hellevik *et al.* 2009, Chen *et al.* 2013*a*, Chan *et al.* 2017) (n=66,216) and five (Talamini *et al.* 1997, Cristofanilli *et al.* 2005, Hellevik *et al.* 2009, Chen *et al.* 2013*a*, Chan *et al.* 2017) (n=26,572) studies, respectively. Most studies had low-to-moderate risk of bias in terms of participants' selection and exposure/outcome ascertainment. However, except in two studies (Cristofanilli *et al.* 2005, Chan *et al.* 2017), no adjustment was made for potential confounders such as hormone replacement therapy/menopausal status, parity, or family history of breast cancer. Except one study reporting only one cancer case among the exposed (Chan *et al.* 2017), all other studies reported statistically significant (Metso *et al.* 2007, Chen *et al.* 2013*a*) or non-significant (Goldman *et al.* 1988, Talamini *et al.* 1997, Mellemgaard *et al.* 1998, Hellevik *et al.* 2009) increased risks with hyperthyroidism (Fig. 2). In contrast, most studies found decreased risks with hypothyroidism, though they were based on relatively small numbers of cases and mostly reported statistically non-significant associations (Fig. 3). This decrease was statistically significant in only one large study which considered adjustment for important potential confounders such as family history of breast cancer, hormone replacement therapy, and menopausal status (Cristofanilli *et al.* 2005).

The pooled risk ratio was 1.20 (95%CI: 1.04 to 1.38, 557 cases among the exposed) for hyperthyroidism, with weak evidence of heterogeneity (I^2=27%, P=0.22), and 0.73 (95%CI 0.43 to 1.24, 144 cases among the exposed) for hypothyroidism, but with a substantial degree of heterogeneity (I^2=77%, P<0.01). However, the only study reporting a positive association with hypothyroidism had no information on potential confounders (Chen *et al.* 2013*b*). Among the other studies, the risk estimates were relatively consistent, and the most influential study (Supplementary Fig. 18) accounted for important breast cancer risk factors (Cristofanilli *et al.* 2005).

The risk ratio associated with hyperthyroidism was higher among women treated with RAI only (risk ratio=1.54, 95%CI 1.08 to 2.19) (Metso *et al.* 2007) than in untreated women (risk ratio=0.82, 95%CI 0.24 to 2.81) (Hellevik *et al.* 2009, Chan *et al.* 2017). Nevertheless, the difference by different treatment subgroups was not statistically significant ($p_{heterogeneity}$=0.54, Supplementary Fig. 9). In contrast, breast cancer risk significantly decreased among women treated with THRT (risk ratio=0.44, 95%CI 0.32 to 0.60) (Cristofanilli *et al.* 2005), whereas no significant association with hypothyroidism was found among untreated women (risk ratio=0.82, 95%CI 0.56 to 1.21) (Hellevik *et al.* 2009, Chan *et al.* 2017) ($p_{heterogeneity}$ among treatment subgroups=0.03, Supplementary Fig. 12).

Prostate cancer

Six (Mellemgaard *et al.* 1998, Metso *et al.* 2007, Hellevik *et al.* 2009, Mondul *et al.* 2012, Chen *et al.* 2013*a*, Chan *et al.* 2017) (n=14,891) and four (Hellevik *et al.* 2009, Mondul *et al.* 2012, Chen *et al.* 2013*b*, Chan *et al.*

https://erc.bioscientifica.com
https://doi.org/10.1530/ERC-19-0417

2017) (n=41,272) studies reported risks associated with hyperthyroidism and hypothyroidism, respectively. Risk of prostate cancer was significantly (Hellevik *et al.* 2009) or non-significantly (Mellemgaard *et al.* 1998, Metso *et al.* 2007, Chen *et al.* 2013*a*, Chan *et al.* 2017) increased with hyperthyroidism in five cohorts (Fig. 2). In contrast, except in one study reporting only one cancer case in the exposed (Chen *et al.* 2013*b*), the risk decreased with hypothyroidism in the three other studies (Hellevik *et al.* 2009, Mondul *et al.* 2012, Chan *et al.* 2017), one of which reached statistical significance (risk ratio=0.48, 95%CI 0.28 to 0.81) (Supplementary Table 2).

The pooled risk ratio for hyperthyroidism was 1.35 (95%CI 1.05 to 1.74, 92 cases among the exposed), with no evidence of heterogeneity (I^2=0%, P=0.60), based on studies with low risk of bias for participants' selection and exposure/outcome ascertainment. However, this risk estimate was mostly unadjusted for important potential confounders, such as family history of cancer, ethnicity, and BMI (Mellemgaard *et al.* 1998, Metso *et al.* 2007, Hellevik *et al.* 2009, Chen *et al.* 2013*a*, Chan *et al.* 2017). Furthermore, the risk ratio varied across subgroups. In particular, it was higher in untreated men (risk ratio=1.94, 95%CI 1.13 to 3.34) (Hellevik *et al.* 2009, Chan *et al.* 2017) than in those treated by RAI (risk ratio=1.50, 95%CI 0.79 to 2.85) (Metso *et al.* 2007), even though the difference among different treatment subgroups was not significant ($p_{heterogeneity}$=0.27, Supplementary Table 10). Given the limited number of studies, we combined the published risk estimates for hypothyroidism with a random-effect model, for exploratory purposes, and found a pooled risk ratio of 0.70 (95%CI 0.45 to 1.07, 46 cases among the exposed) with a low level of heterogeneity (I^2=23%, P=0.3).

Respiratory tract cancer

A total of 121,616 individuals were included in seven cohorts on hyperthyroidism (Goldman *et al.* 1988, Mellemgaard *et al.* 1998, Metso *et al.* 2007, Hellevik *et al.* 2009, Chen *et al.* 2013*a*, Yeh *et al.* 2013, Chan *et al.* 2017). Two studies indicated a significantly increased risk (Mellemgaard *et al.* 1998, Hellevik *et al.* 2009), while the five others did not show any association based on the few cases (Fig. 2). The pooled risk ratio was 1.06 (95%CI 0.80 to 1.42, 262 cases among the exposed), with weak evidence of heterogeneity (I^2=39%, P=0.13). Heterogeneity was possibly explained by a study reporting a 2-fold higher risk among hyperthyroid individuals (Hellevik *et al.* 2009), while the others found no association or a marginally increased risk (Supplementary Fig. 16). All but two (Goldman *et al.* 1988, Metso *et al.* 2007) studies had moderate-to-low risk of bias in terms of participants' selection and outcome ascertainment, but most studies lacked data on potential confounding factors such as smoking history and family history of cancer (Goldman *et al.* 1988, Mellemgaard *et al.* 1998, Metso *et al.* 2007, Chen *et al.* 2013*a*, Yeh *et al.* 2013). The pooled risk ratio restricted to the two studies providing estimates adjusted for important confounding factors, including smoking, was 2.13 (95%CI 1.17 to 3.90, 12 cases among the exposed) (Hellevik *et al.* 2009, Chan *et al.* 2017) (Supplementary Table 6). The results did not statistically differ between the three studies reporting risks restricted to lung cancer and the four studies investigating all respiratory tract cancers combined (P=0.81, Supplementary Table 6). However, they varied according to hyperthyroidism treatment modalities, with a pooled risk ratio of 1.42 (95%CI 0.70 to 2.88) among untreated individuals (Hellevik *et al.* 2009, Yeh *et al.* 2013, Chan *et al.* 2017) and 0.85 (95%CI 0.48 to 1.52) among individuals treated with RAI (Metso *et al.* 2007), but the difference by different treatment subgroups was not significant ($p_{heterogeneity}$=0.47, Supplementary Fig. 11). Of three studies investigating the association between hypothyroidism and respiratory tract cancer risk, one study reported a non-significantly decreased risk of 0.87 (95%CI 0.43 to 1.74) (Hellevik *et al.* 2009) and two others reported no cancer case in the exposed group (Chen *et al.* 2013, Chan *et al.* 2017).

Other outcomes

Risk estimates from individual studies on other cancer sites are reported in Supplementary Tables 1 and 2. Two large case-control studies reported significantly increased risks of extra- and/or intra-hepatic cholangiocarcinoma with hyperthyroidism, based on a total of 162 cases among the exposed (Welzel *et al.* 2007, Petrick *et al.* 2017). Two other studies reported non-significantly elevated liver cancer risks in hyperthyroid individuals, based on only 13 and 8 cases respectively (Hassan *et al.* 2009, Chen *et al.* 2013*a*). The estimated liver cancer risks with hypothyroidism were inconsistent across studies (Hassan *et al.* 2009, Chen *et al.* 2013*b*). We also identified three studies investigating brain cancer risk, which suggested an increased risk (varying from 1.3 to 2.3) with hyperthyroidism (Goldman *et al.* 1988, Mellemgaard *et al.* 1998, Metso *et al.* 2007) based on a few cases. No study provided results on the hypothyroidism-brain cancer risk association. Renal cancer risk also appeared elevated among hyperthyroid individuals (Mellemgaard *et al.* 1998, Metso *et al.* 2007, Chen *et al.* 2013*a*), with significantly

https://erc.bioscientifica.com
https://doi.org/10.1530/ERC-19-0417

increased risks in two studies (risk ratio = 2.32, 95%CI: 1.06 to 5.01, 20 cases among the exposed (Metso *et al.* 2007); risk ratio = 1.3, 95%CI: 1.0 to 1.8, 44 cases among the exposed (Mellemgaard *et al.* 1998)). Last, two studies reported a non-significantly decreased risk ratio (varying from 0.8 to 0.9) of skin cancer associated with hyperthyroidism (Mellemgaard *et al.* 1998, Metso *et al.* 2007). Very little data were available for other outcomes.

Other sensitivity and subgroup analyses

No substantial difference in the estimated risk ratios was observed between random- and fixed-effect models (Supplementary Tables 3, 4, 5 and 6). For all outcomes and exposure groups, cohorts yielded higher risk ratios than case-control studies. The pooled risk ratios for breast and thyroid cancers were also higher in studies where thyroid dysfunction was assessed through hospital or health insurance databases compared to studies using blood measurements or self-reported data. Subsequently, studies conducted in Europe reported the smallest risk estimates for all outcomes, while those conducted in Asia yielded the highest risk estimates. However, pooled risk ratios did not statistically differ among regions, with the exception of breast cancer after hypothyroidism. Other sensitivity-, subgroup-, and influence analyses did not substantially modify the results (Supplementary Figs 13, 14, 15, 17 and Supplementary Tables 3, 4, 5, 6).

Discussion

This systematic review uncovered several studies evaluating the relationship between thyroid dysfunction, mostly as overt disorder, and cancer risk by tumor site, including thyroid, breast, prostate, respiratory tract, liver, brain, kidney, and skin cancers. Our meta-analysis of 15 cohort and case-control studies showed that hyperthyroidism was associated with 20%, 35%, and 4.5-fold higher risks of breast, prostate, and thyroid cancer, respectively, compared to euthyroidism. We found no clear evidence of an association between hyperthyroidism and other site-specific cancer risks, based on very few studies. Hypothyroidism was significantly associated with a 3-fold higher risk of thyroid cancer, which was limited to the first 10 years after diagnosis of hypothyroidism. Hypothyroidism was not significantly associated with risk of other cancer sites, including breast and prostate cancers.

While previous reviews focused on thyroid and breast cancers (Sarlis *et al.* 2002, Angelousi *et al.* 2012, Hardefeldt *et al.* 2012, Fang *et al.* 2017), the present review is the first one to report associations between hyperthyroidism and hypothyroidism and risk of a wide range of cancer types and pooled risk estimates for prostate and respiratory tract cancers. Our findings are partly consistent with previous meta-analyses. A previous meta-analysis of 12 case-control studies published through 1997 reported an increased thyroid cancer risk associated with self-reported hyperthyroidism (diagnosed at least one year prior to cancer diagnosis) in both women (risk ratio = 1.4, 95%CI: 1.0 to 2.1) and men (risk ratio = 3.1, 95%CI: 1.0 to 9.8), but not with hypothyroidism (Franceschi *et al.* 1999). This study found weaker associations for both types of thyroid dysfunction compared to ours. This might be explained by differing practices in the management of hyperthyroidism according to age and country. Treatment of hyperthyroidism, especially when using radioactive iodine, often results in hypothyroidism. This may thus lead to somewhat confounded risk associations with hypothyroidism in the most recent studies, due to a higher proportion of hypothyroid individuals who were previously treated for hyperthyroidism than in the past studies. Moreover, most recent studies may benefit from a better thyroid dysfunction diagnosis and/or enhanced cancer surveillance strategies in the most recent years. Indeed, there is now evidence that increased TSH levels is a marker of thyroid cancer among patients with nodules, with a dose-response relationship (McLeod *et al.* 2012, Hu *et al.* 2016). Our results are compatible with recent findings of an inverse association between prediagnosis TSH levels and thyroid cancer risk in a healthy population (Rinaldi *et al.* 2014) and common genetic variants for low TSH levels and thyroid cancer (Gudmundsson *et al.* 2012).

Unlike previous meta-analyses (Hardefeldt *et al.* 2012, Fang *et al.* 2017), we found a significantly increased risk of breast cancer with hyperthyroidism after inclusion of a recent, large longitudinal study (Chen *et al.* 2013*a*) and exclusion of studies with prevalent cancers where thyroid dysfunction might result from cancer symptoms or treatment toxicities. Our findings are compatible with two recent large cohort studies reporting an elevated breast cancer risk in relation to increasing T4 and T3 levels within normal ranges (Tosovic *et al.* 2010, 2012). They are also consistent with previous meta-analyses which reported no association between hypothyroidism and breast cancer risk (Angelousi *et al.* 2012).

High heterogeneity across individual studies was observed for thyroid and breast cancers, but not for other cancer sites. Risk estimates widely varied across studies in terms of magnitude of thyroid cancer risk with hyperthyroidism (risk ratios ranging from 1.7 to 10.4)

https://erc.bioscientifica.com
https://doi.org/10.1530/ERC-19-0417

or hypothyroidism (risk ratios ranging from 1.8 to 11.8), and in terms of direction of the association between hypothyroidism and breast cancer. The different ascertainment methods of thyroid dysfunction across studies is probably one factor explaining this heterogeneity, since higher risks were estimated in studies based on hospital or health insurance data compared to population-based studies using blood measurements or self-reported data. The different risk estimates between hospital- and population-based studies may also reflect different severity degrees of thyroid dysfunction or comorbidities – but data were lacking to investigate this hypothesis. Differences in potential confounding factors, for example, calendar year, family cancer history, or menopausal status, can also account for some heterogeneity, but these data were lacking in many studies (Talamini *et al.* 1997, Memon *et al.* 2002, Metso *et al.* 2007, Hellevik *et al.* 2009, Chen *et al.* 2013*a*,*b*), particularly in those based on health insurance databases.

Biological mechanisms underlying associations between thyroid dysfunction and cancer are not well known, but a number of hypotheses have been suggested in *in vitro* and *in vivo* studies. TSH has been found to stimulate follicular thyroid cell growth and differentiation (Hard 1998). T3 and T4 can be anti-apoptotic and have a proliferative effect on thyroid, breast, and prostate cancer cell lines by regulating gene expression (TGF-α, B-cell translocation gene 2) (Tsui *et al.* 2008, Pinto *et al.* 2011), causing phosphorylation by MAPK pathways, binding in the integrin αvβ3 (Moeller & Führer 2013, Hercbergs *et al.* 2018), and stimulating estrogen-like effects (Dinda *et al.* 2002). Moreover, excessive or insufficient iodine intake, which plays a key role in thyroid hormone production, could also be a risk factor of breast and thyroid cancers (Dong *et al.* 2018). Current experimental evidence thus support epidemiological findings on a positive association between hyperthyroidism and cancer risk.

Nonetheless, the interpretation of those findings as a causal relationship between hyperthyroidism and cancer incidence is not straightforward. Indeed, thyroid dysfunction can be subsequent to cancer or cancer treatments. Our study minimized the possibility of reverse causation by excluding prevalent or previous cancer cases at the time of thyroid dysfunction diagnosis/detection. However, the decreased pooled risk ratios of thyroid cancer with time since thyroid dysfunction diagnosis/detection (Fig. 4) are suggestive of a surveillance bias (e.g. incidental cancer cases detected by thyroidectomy for hyperthyroidism treatment) in the first years of follow-up. Nevertheless, while thyroid cancer risk was no longer increased in hypothyroid individuals after 10 years of follow-up, it remained significantly increased in hyperthyroid individuals with a risk ratio of 2.50 (95%CI: 1.66 to 3.78) compared to euthyroid individuals. Unfortunately, few studies have reported data on tumor histology (Huang *et al.* 2017, Kitahara *et al.* 2018), size (Cristofanilli *et al.* 2005, Huang *et al.* 2017) and stage at diagnosis (Cristofanilli *et al.* 2005, Kitahara *et al.* 2018), which could strengthen the assessment of a potential surveillance bias. Though risk factors (e.g. iodine intake, radiation exposure) and age at diagnosis differ according to thyroid cancer histology (Aschebrook-Kilfoy *et al.* 2013, Liu *et al.* 2017), Kitahara *et al.* (2018) found very similar thyroid dysfunction-related risks for papillary and follicular thyroid cancers. The authors nevertheless reported a higher hyperthyroidism-related risk for localized thyroid cancer than regional/distant thyroid cancer as compared to the general population, which suggests that a certain proportion of, but not all, the increased risk related to hyperthyroidism may be due to a surveillance bias. This study also showed a non-significantly increased risk of localized thyroid cancer with hypothyroidism, but no association for regional/distant cancer (based on very few cancer cases), which is also indicative of a surveillance bias. Similarly, Cristofanilli *et al.* (2005) found that, among women diagnosed with breast cancer, hypothyroid women were more frequently diagnosed with an early-stage or small-size (≤2 cm) tumor than euthyroid women. Current evidence thus suggest that part of the thyroid dysfunction-related excess risks may be associated with non-clinically relevant thyroid and breast cancers, but this should be confirmed (Staniforth *et al.* 2016, Lim *et al.* 2017). The remaining elevated risk, 10 years after thyroid dysfunction diagnosis/detection, may also reflect the effect of underlying autoimmune diseases, which are associated with increased risk of thyroid and breast cancer (Shu *et al.* 2010, Resende de Paiva *et al.* 2017).

The estimated cancer risks could have also been mediated or modified by thyroid dysfunction treatments. Indeed, our results show differences in risk estimates by treatment modalities (Supplementary Figs 8, 9, 10, 11 and 12), for example, hypothyroid women treated with THRT had a reduced risk of breast cancer, whereas no significant association was found among untreated hypothyroid women. However, very few studies contributed to the analyses stratified by treatments, and treatment-specific risk estimates were available only for RAI and THRT, which was insufficient for the interpretation of the role of thyroid dysfunction treatments in the relationship between thyroid dysfunction and cancer risk.

https://erc.bioscientifica.com
https://doi.org/10.1530/ERC-19-0417

Moreover, as the populations may differ in many other aspects than treatments, it remains very difficult to disentangle whether those differences reflect the impact of the treatment itself, its impact on thyroid dysfunction, or different severities of thyroid dysfunction and associated comorbidities.

The present study has several strengths. We conducted an extensive and systematic literature search on the association between both hyper- and hypothyroidism and cancer risk, with no restriction to cancer type. This enabled us to report results on cancer sites that have not been considered in previous meta-analyses (e.g. prostate and respiratory tract cancer) and investigate the possible role of thyroid hormones for hormone-dependent (e.g. thyroid, breast, and prostate cancers) and non-hormone-dependent cancers (e.g. respiratory tract cancer). Unlike previous meta-analyses, we applied no restriction on the method for thyroid dysfunction ascertainment to retrieve a maximal number of relevant publications. However, we excluded studies with cancer history prior to thyroid dysfunction diagnosis/detection to minimize the possibility of reverse causation. Subgroup and sensitivity analyses were conducted to explore potential factors that could explain heterogeneity of results

There are also several limitations to our study. Firstly, data on treatments and important potential confounding factors (e.g. family history of cancer, BMI, and reproductive factors) were lacking in most studies, which prevented us from investigating their impact on the risk estimates. In addition, even though information was available on time since thyroid dysfunction diagnosis/detection, no data were available on the duration of overt dysfunctional state and status after thyroid dysfunction treatment (e.g. euthyroidism or hypothyroidism after treatment for hyperthyroidism). Secondly, high levels of heterogeneity were found for thyroid cancer after hypo- or hyperthyroidism and breast cancer after hypothyroidism. Outliers were also observed in the analysis of follow-up time. This questions the robustness of the pooled risk estimates. Last, different measures of association (relative risk, odds ratio, hazard ratio, and standardized incidence ratio) were pooled together, which involves the following assumptions: rare outcome (for odds ratio and hazard ratio), no association between the exposure and censoring status (for hazard ratio), and the use of data from the general population as a comparison group (for standardized incidence ratio) (Goldman *et al.* 1988, Mellemgaard *et al.* 1998, Kitahara *et al.* 2018), which were nevertheless verified for most studies.

In conclusion, current evidence from epidemiological studies showed that hyperthyroidism is associated with increased risks of thyroid, breast, and prostate cancers, compared to euthyroidism. Hypothyroidism is associated with an increased risk of thyroid cancer within the first 10 years of follow-up. However, it remains unclear whether these findings represent causal relationships because information on important potential confounders, thyroid dysfunction treatments, associated comorbidities, underlying disease, cancer stage at diagnosis, and histology was lacking in most studies. Further prospective studies should investigate possible confounding or mediating effects of treatments, comorbidities, and major cancer risk factors on the associations between thyroid dysfunction and cancer risk.

Supplementary materials

This is linked to the online version of the paper at https://doi.org/10.1530/ERC-19-0417.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding

Thi-Van-Trinh Tran received a doctoral grant from the Paris Sud-Paris Saclay University.

Ethics approval and consent to participate

This systematic review and meta-analysis only used published data, with no access to individual data. No ethical approval or participants' consent to participate was thus required for this study.

Data availability

All data reported in this manuscript can be found in the original articles mentioned in the list of references.

Author contribution statement

T T V T and N J designed the study protocol, performed the literature search, extracted data from the original articles and assessed risk of biases of the included studies, and drafted the first version of the manuscript. T T V T conducted the statistical analyses. C M K, F D, and M C B R contributed to the interpretation of the results and the drafting of the paper. All co-authors approved the publication of the manuscript in its final version.

References

Angelousi AG, Anagnostou VK, Stamatakos MK, Georgiopoulos GA & Kontzoglou KC 2012 MECHANISMS IN ENDOCRINOLOGY: Primary HT and risk for breast cancer: a systematic review and meta-analysis. *European Journal of Endocrinology* **166** 373–381. (https://doi.org/10.1530/EJE-11-0838)

Aschebrook-Kilfoy B, Grogan RH, Ward MH, Kaplan E & Devesa SS 2013 Follicular thyroid cancer incidence patterns in the United States, 1980–2009. *Thyroid* **23** 1015–1021. (https://doi.org/10.1089/thy.2012.0356)

Balasubramaniam S, Ron E, Gridley G, Schneider AB & Brenner AV 2012 Association between benign thyroid and endocrine disorders and subsequent risk of thyroid cancer among 4.5 million US male veterans. *Journal of Clinical Endocrinology and Metabolism* **97** 2661–2669. (https://doi.org/10.1210/jc.2011-2996)

Brandt F, Thvilum M, Almind D, Christensen K, Green A, Hegedüs L & Brix TH 2013 Morbidity before and after the diagnosis of hyperthyroidism: a nationwide register-based study. *PLoS ONE* **8** e66711. (https://doi.org/10.1371/journal.pone.0066711)

Chan YX, Knuiman MW, Divitini ML, Brown SJ, Walsh J & Yeap BB 2017 Lower TSH and higher free thyroxine predict incidence of prostate but not breast, colorectal or lung cancer. *European Journal of Endocrinology* **177** 297–308. (https://doi.org/10.1530/EJE-17-0197)

Chen YK, Lin CL, Chang YJ, Cheng FT-F, Peng CL, Sung FC, Cheng YH & Kao CH 2013*a* Cancer risk in patients with Graves' disease: a nationwide cohort study. *Thyroid* **23** 879–884. (https://doi.org/10.1089/thy.2012.0568)

Chen YK, Lin CL, Cheng FT, Sung FC & Kao CH 2013*b* Cancer risk in patients with Hashimoto's thyroiditis: a nationwide cohort study. *British Journal of Cancer* **109** 2496–2501. (https://doi.org/10.1038/bjc.2013.597)

Cristofanilli M, Yamamura Y, Kau SW, Bevers T, Strom S, Patangan M, Hsu L, Krishnamurthy S, Theriault RL & Hortobagyi GN 2005 Thyroid hormone and breast carcinoma: primary hypothyroidism is associated with a reduced incidence of primary breast carcinoma. *Cancer* **103** 1122–1128. (https://doi.org/10.1002/cncr.20881)

DerSimonian R & Laird N 1986 Meta-analysis in clinical trials. *Controlled Clinical Trials* **7** 177–188. (https://doi.org/10.1016/0197-2456(86)90046-2)

Dinda S, Sanchez A & Moudgil V 2002 Estrogen-like effects of thyroid hormone on the regulation of tumor suppressor proteins, p53 and retinoblastoma, in breast cancer cells. *Oncogene* **21** 761–768. (https://doi.org/10.1038/sj.onc.1205136)

Dong L, Lu J, Zhao B, Wang W & Zhao Y 2018 Review of the possible association between thyroid and breast carcinoma. *World Journal of Surgical Oncology* **16** 130. (https://doi.org/10.1186/s12957-018-1436-0)

Egger M, Smith GD, Schneider M & Minder C 1997 Bias in meta-analysis detected by a simple, graphical test. *BMJ* **315** 629–634. (https://doi.org/10.1136/bmj.315.7109.629)

Fang Y, Yao L, Sun J, Yang R, Chen Y, Tian J, Yang K & Tian L 2017 Does thyroid dysfunction increase the risk of breast cancer? A systematic review and meta-analysis. *Journal of Endocrinological Investigation* **40** 1035–1047. (https://doi.org/10.1007/s40618-017-0679-x)

Forman D, Bray F, Brewster D, Gombe Mbalawa C, Kohler B, Piñeros M, Steliarova-Foucher E, Swaminathan R & Ferlay J 2013 Cancer incidence in five continents, Vol. X. Lyon, France: IARC. (available at: http://ci5.iarc.fr/CI5-X/Default.aspx)

Franceschi S, Preston-Martin S, Dal Maso L, Negri E, La Vecchia C, Mack WJ, McTiernan A, Kolonel L, Mark SD, Mabuchi K, *et al.* 1999 A pooled analysis of case–control studies of thyroid cancer. IV. Benign thyroid diseases. *Cancer Causes and Control* **10** 583–595. (https://doi.org/10.1023/a:1008907227706)

Garmendia Madariaga A, Santos Palacios S, Guillén-Grima F & Galofré JC 2014 The incidence and prevalence of thyroid dysfunction in Europe: a meta-analysis. *Journal of Clinical Endocrinology and Metabolism* **99** 923–931. (https://doi.org/10.1210/jc.2013-2409)

Goldman MB, Maloof F, Monson RR, Aschengrau A, Cooper DS & Ridgway EC 1988 Radioactive iodine therapy and breast cancer: a follow-up study of hyperthyroid women. *American Journal of Epidemiology* **127** 969–980. (https://doi.org/10.1093/oxfordjournals.aje.a114900)

Gudmundsson J, Sulem P, Gudbjartsson DF, Jonasson JG, Masson G, He H, Jonasdottir A, Sigurdsson A, Stacey SN, Johannsdottir H, *et al.* 2012 Discovery of common variants associated with low TSH levels and thyroid cancer risk. *Nature Genetics* **44** 319–322. (https://doi.org/10.1038/ng.1046)

Hard GC 1998 Recent developments in the investigation of thyroid regulation and thyroid carcinogenesis. *Environmental Health Perspectives* **106** 427–436. (https://doi.org/10.1289/ehp.106-1533202)

Hardefeldt PJ, Eslick GD & Edirimanne S 2012 Benign thyroid disease is associated with breast cancer: a meta-analysis. *Breast Cancer Research and Treatment* **133** 1169–1177. (https://doi.org/10.1007/s10549-012-2019-3)

Hassan MM, Kaseb A, Li D, Patt YZ, Vauthey JN, Thomas MB, Curley SA, Spitz MR, Sherman SI, Abdalla EK, *et al.* 2009 Association between hypothyroidism and hepatocellular carcinoma: a case-control study in the United States. *Hepatology* **49** 1563–1570. (https://doi.org/10.1002/hep.22793)

Hellevik AI, Åsvold BO, Bjøro T, Romundstad PR, Nilsen TIL & Vatten LJ 2009 Thyroid function and cancer risk: a prospective population study. *Cancer Epidemiology, Biomarkers and Prevention* **18** 570–574. (https://doi.org/10.1158/1055-9965.EPI-08-0911)

Hercbergs A, Mousa SA, Leinung M, Lin HY & Davis PJ 2018 Thyroid hormone in the clinic and breast cancer. *Hormones and Cancer* **9** 139–143. (https://doi.org/10.1007/s12672-018-0326-9)

Higgins JP & Thompson SG 2002 Quantifying heterogeneity in a meta-analysis. *Statistics in Medicine* **21** 1539–1558. (https://doi.org/10.1002/sim.1186)

Hu N, Li ZM, Liu JF, Zhang ZZ & Wang LS 2016 An overall and dose-response meta-analysis for thyrotropin and thyroid cancer risk by histological type. *Oncotarget* **7** 47750–47759. (https://doi.org/10.18632/oncotarget.10282)

Huang H, Rusiecki J, Zhao N, Chen Y, Ma S, Yu H, Ward MH, Udelsman R & Zhang Y 2017 Thyroid-stimulating hormone, thyroid hormones, and risk of papillary thyroid cancer: a nested case–control study. *Cancer Epidemiology, Biomarkers and Prevention* **26** 1209–1218. (https://doi.org/10.1158/1055-9965.EPI-16-0845)

Journy NMY, Bernier MO, Doody MM, Alexander BH, Linet MS & Kitahara CM 2017 Hyperthyroidism, hypothyroidism, and cause-specific mortality in a large cohort of women. *Thyroid* **27** 1001–1010. (https://doi.org/10.1089/thy.2017.0063)

Kang JH, Kueck AS, Stevens R, Curhan G, De Vivo I, Rosner B, Alexander E & Tworoger SS 2013 A large cohort study of hypothyroidism and hyperthyroidism in relation to gynecologic cancers. *Obstetrics and Gynecology International* **2013** 743721. (https://doi.org/10.1155/2013/743721)

Kitahara CM, Körmendiné Farkas D, Jørgensen JOL, Cronin-Fenton D & Sørensen HT 2018 Benign thyroid diseases and risk of thyroid cancer: a nationwide cohort study. *Journal of Clinical Endocrinology and Metabolism* **103** 2216–2224. (https://doi.org/10.1210/jc.2017-02599)

Laurberg P, Knudsen N, Andersen S, Carlé A, Pedersen IB & Karmisholt J 2012 Thyroid function and obesity. *European Thyroid Journal* **1** 159–167. (https://doi.org/10.1159/000342994)

Lim H, Devesa SS, Sosa JA, Check D & Kitahara CM 2017 Trends in thyroid cancer incidence and mortality in the United States, 1974–2013. *JAMA* **317** 1338–1348. (https://doi.org/10.1001/jama.2017.2719)

Liu Y, Su L & Xiao H 2017 Review of factors related to the thyroid cancer epidemic. *International Journal of Endocrinology* **2017** 5308635. (https://doi.org/10.1155/2017/5308635)

McLeod DS, Watters KF, Carpenter AD, Ladenson PW, Cooper DS & Ding EL 2012 Thyrotropin and thyroid cancer diagnosis: a systematic review and dose-response meta-analysis. *Journal of Clinical Endocrinology and Metabolism* **97** 2682–2692. (https://doi.org/10.1210/jc.2012-1083)

Mellemgaard A, From G, Jørgensen T, Johansen C, Olsen JH & Perrild H 1998 Cancer risk in individuals with benign thyroid disorders. *Thyroid* **8** 751–754. (https://doi.org/10.1089/thy.1998.8.751)

Memon A, Varghese A & Suresh A 2002 Benign thyroid disease and dietary factors in thyroid cancer: a case–control study in Kuwait. *British Journal of Cancer* **86** 1745–1750. (https://doi.org/10.1038/sj.bjc.6600303)

Metso S, Auvinen A, Huhtala H, Salmi J, Oksala H & Jaatinen P 2007 Increased cancer incidence after radioiodine treatment for hyperthyroidism. *Cancer* **109** 1972–1979. (https://doi.org/10.1002/cncr.22635)

Minlikeeva AN, Freudenheim JL, Cannioto RA, Eng KH, Szender JB, Mayor P, Etter JL, Cramer DW, Diergaarde B, Doherty JA, *et al.* 2017 History of thyroid disease and survival of ovarian cancer patients: results from the Ovarian Cancer Association Consortium, a brief report. *British Journal of Cancer* **117** 1063–1069. (https://doi.org/10.1038/bjc.2017.267)

Moeller LC & Führer D 2013 Thyroid hormone, thyroid hormone receptors, and cancer: a clinical perspective. *Endocrine-Related Cancer* **20** R19–R29. (https://doi.org/10.1530/ERC-12-0219)

Moher D, Liberati A, Tetzlaff J, Altman DG & PRISMA Group 2009 Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Annals of Internal Medicine* **151** 264–249. (https://doi.org/10.7326/0003-4819-151-4-200908180-00135)

Mondul AM, Weinstein SJ, Bosworth T, Remaley AT, Virtamo J & Albanes D 2012 Circulating thyroxine, thyroid-stimulating hormone, and hypothyroid status and the risk of prostate cancer. *PLoS ONE* **7** e47730. (https://doi.org/10.1371/journal.pone.0047730)

Munoz JM, Gorman CA, Elveback LR & Wentz JR 1978 Incidence of malignant neoplasms of all types in patients with Graves' disease. *Archives of Internal Medicine* **138** 944–947. (https://doi.org/10.1001/archinte.1978.03630310034015)

Petitti DB 2001 Approaches to heterogeneity in meta-analysis. *Statistics in Medicine* **20** 3625–3633. (https://doi.org/10.1002/sim.1091)

Petrick JL, Yang B, Altekruse SF, Van Dyke AL, Koshiol J, Graubard BI & McGlynn KA 2017 Risk factors for intrahepatic and extrahepatic cholangiocarcinoma in the United States: a population-based study in SEER-Medicare. *PLoS ONE* **12** e0186643. (https://doi.org/10.1371/journal.pone.0186643)

Pinto M, Soares P & Ribatti D 2011 Thyroid hormone as a regulator of tumor induced angiogenesis. *Cancer Letters* **301** 119–126. (https://doi.org/10.1016/j.canlet.2010.11.011)

Resende de Paiva C, Grønhøj C, Feldt-Rasmussen U & von Buchwald C 2017 Association between Hashimoto's thyroiditis and thyroid cancer in 64,628 patients. *Frontiers in Oncology* **7** 53–53. (https://doi.org/10.3389/fonc.2017.00053)

Rinaldi S, Plummer M, Biessy C, Tsilidis KK, Østergaard JN, Overvad K, Tjønneland A, Halkjær J, Boutron-Ruault MC, Clavel-Chapelon F, *et al.* 2014 Thyroid-stimulating hormone, thyroglobulin, and thyroid hormones and risk of differentiated thyroid carcinoma: the EPIC study. *Journal of the National Cancer Institute* **106** dju097. (https://doi.org/10.1093/jnci/dju097)

Sandhu MK, Brezden-Masley C, Lipscombe LL, Zagorski B & Booth GL 2009 Autoimmune hypothyroidism and breast cancer in the elderly. *Breast Cancer Research and Treatment* **115** 635–641. (https://doi.org/10.1007/s10549-008-0104-4)

Sarfati D, Koczwara B & Jackson C 2016 The impact of comorbidity on cancer and its treatment. *CA: A Cancer Journal for Clinicians* **66** 337–350. (https://doi.org/10.3322/caac.21342)

Sarlis NJ, Gourgiotis L, Pucino F & Tolis GJ 2002 Lack of association between Hashimoto thyroiditis and breast cancer: a quantitative research synthesis. *Hormones* **1** 35–41. (https://doi.org/10.14310/horm.2002.1152)

Shu X, Ji J, Li X, Sundquist J, Sundquist K & Hemminki K 2010 Cancer risk in patients hospitalised for Graves' disease: a population-based cohort study in Sweden. *British Journal of Cancer* **102** 1397–1399. (https://doi.org/10.1038/sj.bjc.6605624)

Søgaard M, Farkas DK, Ehrenstein V, Jørgensen JOL, Dekkers OM & Sørensen HT 2016 Hypothyroidism and hyperthyroidism and breast cancer risk: a nationwide cohort study. *European Journal of Endocrinology* **174** 409–414. (https://doi.org/10.1530/EJE-15-0989)

Staniforth JU, Erdirimanne S & Eslick GD 2016 Thyroid carcinoma in Graves' disease: a meta-analysis. *International Journal of Surgery* **27** 118–125. (https://doi.org/10.1016/j.ijsu.2015.11.027)

Talamini R, Franceschi S, Favero A, Negri E, Parazzini F & La Vecchia C 1997 Selected medical conditions and risk of breast cancer. *British Journal of Cancer* **75** 1699–1703. (https://doi.org/10.1038/bjc.1997.289)

Thompson SG & Higgins JP 2002 How should meta-regression analyses be undertaken and interpreted? *Statistics in Medicine* **21** 1559–1573. (https://doi.org/10.1002/sim.1187)

Tosovic A, Bondeson AG, Bondeson L, Ericsson UB, Malm J & Manjer J 2010 Prospectively measured triiodothyronine levels are positively associated with breast cancer risk in postmenopausal women. *Breast Cancer Research* **12** R33. (https://doi.org/10.1186/bcr2587)

Tosovic A, Becker C, Bondeson AG, Bondeson L, Ericsson UB, Malm J & Manjer J 2012 Prospectively measured thyroid hormones and thyroid peroxidase antibodies in relation to breast cancer risk. *International Journal of Cancer* **131** 2126–2133. (https://doi.org/10.1002/ijc.27470)

Tsui KH, Hsieh WC, Lin MH, Chang PL & Juang HH 2008 Triiodothyronine modulates cell proliferation of human prostatic carcinoma cells by downregulation of the B-cell translocation gene 2. *Prostate* **68** 610–619. (https://doi.org/10.1002/pros.20725)

Viechtbauer W & Cheung MWL 2010 Outlier and influence diagnostics for meta-analysis. *Research Synthesis Methods* **1** 112–125. (https://doi.org/10.1002/jrsm.11)

Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M & Tugwell P 2001 The Newcastle-Ottawa Scale (NOS) for assessing the quality of non randomised studies in meta-analyses. Ottowa, Canada: University of Ottawa. (available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp)

Welzel TM, Graubard BI, El-Serag HB, Shaib YH, Hsing AW, Davila JA & McGlynn KA 2007 Risk factors for intrahepatic and extrahepatic cholangiocarcinoma in the United States: a population-based case-control study. *Clinical Gastroenterology and Hepatology* **5** 1221–1228. (https://doi.org/10.1016/j.cgh.2007.05.020)

Yeh NC, Chou CW, Weng SF, Yang CY, Yen FC, Lee SY, Wang JJ & Tien KJ 2013 Hyperthyroidism and thyroid cancer risk: a population-based cohort study. *Experimental and Clinical Endocrinology and Diabetes* **121** 402–406. (https://doi.org/10.1055/s-0033-1341474)

Received in final form 4 February 2020
Accepted 7 February 2020
Accepted Manuscript published online 10 February 2020

Supplementary Appendix

Appendix 1. PRISMA checklist (page numbers refer to the submitted manuscript)

Appendix 2. Search terms used in the systematic review

Appendix 3. Modified Newcastle-Ottawa for risk of bias assessment

Appendix 4. Overall risk of bias of 20 included studies

Appendix 5. Thyroid dysfunction categorization based on thyroid hormone levels

Appendix 6. Studies on the association between thyroid dysfunction and cancer mortality

Supplementary Figure 1. Funnel plot for publication bias of the meta-analysis studying the association of hyperthyroidism and thyroid cancer risk. Egger test (p=0.65) revealed no evidence of publication bias

Supplementary Figure 2. Funnel plot for publication bias of the meta-analysis studying the association of hyperthyroidism and breast cancer risk. Egger test (p=0.85) revealed no evidence of publication bias

Supplementary Figure 3. Funnel plot for publication bias of the meta-analysis studying the association of hyperthyroidism and prostate cancer risk. Egger test (p=0.41) revealed no evidence of publication bias

Supplementary Figure 4. Funnel plot for publication bias of the meta-analysis studying the association of hyperthyroidism and the risk of respiratory tract cancer. Egger test (p=0.49) revealed no evidence of publication bias

Supplementary Figure 5. Funnel plot for publication bias of the meta-analysis studying the association of hypothyroidism and thyroid cancer risk. Egger test (p=0.53) revealed no evidence of publication bias

Supplementary Figure 6. Funnel plot for publication bias of the meta-analysis studying the association of hypothyroidism and breast cancer risk. Egger test (p=0.66) revealed no evidence of publication bias

Supplementary Figure 7. Subgroup analysis by sex of the association between thyroid dysfunction and thyroid cancer risk. The test found no substantial difference between men and women. A. For hyperthyroidism analysis (p=0.43), B. For hypothyroidism analysis (p=0.10). Overall risk ratios are

displayed as diamonds. The size of each square is proportional to the weight of the study. TC: Thyroid cancer, nr: Not reported, PY: person-year.

Supplementary Figure 8. Subgroup analysis by treatment methods of the association between hyperthyroidism and thyroid cancer risk. The test found no substantial difference among different treatment methods (p=0.22). Overall risk ratios are displayed as diamonds. The size of each square is proportional to the weight of the study. TC: Thyroid cancer, PY: person-year, RAI: Radioactive iodine.

Supplementary Figure 9. Subgroup analysis by treatment methods of the association between hyperthyroidism and breast cancer risk. The test found no substantial difference among different treatment methods (p=0.54). Overall risk ratios are displayed as diamonds. The size of each square is proportional to the weight of the study. BC: Breast cancer, nr: Not reported, PY: person-year, RAI: Radioactive iodine.

Supplementary Figure 10. Subgroup analysis by treatment methods of the association between hyperthyroidism and prostate cancer risk. The test found no substantial difference among different treatment methods (p=0.27). Overall risk ratios are displayed as diamonds. The size of each square is proportional to the weight of the study. PC: Prostate cancer, nr: Not reported, RAI: Radioactive iodine.

Supplementary Figure 11. Subgroup analysis by treatment methods of the association between hyperthyroidism and respiratory tract cancer risk. The test found no substantial difference among different treatment methods (p=0.47). Overall risk ratios are displayed as diamonds. The size of each square is proportional to the weight of the study. RTC: Respiratory tract cancer, nr: Not reported, RAI: Radioactive iodine.

Supplementary Figure 12. Subgroup analysis by treatment methods of the association between hypothyroidism and breast cancer risk. The test found a statistically significant difference among different treatment methods (p=0.03). Overall risk ratios are displayed as diamonds. The size of each square is proportional to the weight of the study. BC: Breast cancer, THRT: Thyroid hormone replacement therapy.

Supplementary Figure 13. Influence analysis of the association between hyperthyroidism and thyroid cancer risk

Supplementary Figure 14. Influence analysis of the association between hyperthyroidism and breast cancer risk

Supplementary Figure 15. Influence analysis of the association between hyperthyroidism and prostate cancer risk

Supplementary Figure 16. Influence analysis of the association between hyperthyroidism and respiratory tract cancer risk

Supplementary Figure 17. Influence analysis of the association between hypothyroidism and thyroid cancer risk

Supplementary Figure 18. Influence analysis of the association between hypothyroidism and breast cancer risk

Supplementary Table 1. Association between hyperthyroidism and the risk of different cancer sites other than thyroid, breast, prostate and respiratory tract cancer. Metso 2007: Results estimated based on a figure reported primary results of the article, exact results were not available.

Supplementary Table 2. Association between hypothyroidism and the risk of different cancer sites other than thyroid and breast cancer

Supplementary Table 3. Subgroup and sensitivity analysis of the association between thyroid dysfunction and thyroid cancer risk

Supplementary Table 4. Subgroup and sensitivity analysis of the association between thyroid dysfunction and breast cancer risk

Supplementary Table 5. Subgroup and sensitivity analysis of the association between hyperthyroidism and prostate cancer risk

Supplementary Table 6. Subgroup and sensitivity analysis of the association between hyperthyroidism and the risk of respiratory tract cancer

Appendix 1. PRISMA checklist (page numbers refer to the manuscript after revision)

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3/4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplementary content, Appendix 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4/5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5/6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6
Section/topic	**#**	**Checklist item**	**Reported on page #**
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6/7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6/7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7, Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	8-13; Supplementary content, Appendix 3
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Figures 2, 3
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	8-13; Figures 2, 3
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	8-13; Supplementary Figures 1-6
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	8-13; Figure 4; Supplementary Figures 7-18; Supplementary Tables 3-6
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	14-18
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	18/19
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	19
FUNDING			

Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	20

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

Appendix 2. Search terms used in the systematic review

MeSH Terms

Pubmed

(((thyroid dysfunction*[Title/Abstract] OR thyroid disease*[Title/Abstract] OR thyroid disorder*[Title/Abstract] OR thyroid function*[Title/Abstract] OR thyroid hormone*[Title/Abstract] OR thyroid condition*[Title/Abstract] OR triiodothyronine[Title/Abstract] OR thyroxine[Title/Abstract] OR thyroid-stimulating hormone[Title/Abstract] OR TSH[Title/Abstract] OR hypothyroid[Title/Abstract] OR hypo-thyroid[Title/Abstract] OR hyperthyroid[Title/Abstract] OR hyper-thyroid[Title/Abstract] OR Grave's disease[Title/Abstract] OR Graves disease[Title/Abstract] OR Graves' disease[Title/Abstract] OR Hashimoto's disease[Title/Abstract] OR Hashimoto disease[Title/Abstract] OR Hashimotos disease[Title/Abstract] OR toxic multinodular goiter[Title/Abstract] OR toxic nodular goiter[Title/Abstract] OR toxic goiter[Title/Abstract] OR toxic adenoma[Title/Abstract] OR toxic thyroid nodule[Title/Abstract] OR toxic nodule[Title/Abstract] OR thyroiditis[Title/Abstract] OR thyrotoxicosis[Title/Abstract]) AND (cancer [Title/Abstract] OR cancers[Title/Abstract] OR tumor[Title/Abstract] OR tumors[Title/Abstract] OR tumour[Title/Abstract] OR tumours[Title/Abstract] OR carcinoma[Title/Abstract] OR carcinomas[Title/Abstract] OR neoplasm[Title/Abstract])) AND humans[MeSH Terms] AND (english[Language] OR french[Language] OR vietnamese[Language]) AND (cohort studies[MeSH terms] OR case-control studies[MeSH terms] OR Observational Studies as Topic[MeSH terms])

Results: 2446 publications

Cochrane

#1: (“thyroid dysfunction*” OR “thyroid disease*” OR “thyroid disorder*” OR “thyroid hormone*” OR “thyroid function*” OR “thyroid condition*” OR triiodothyronine OR thyroxine OR thyroid-stimulating hormone OR TSH OR hypothyroid OR hypo-thyroid OR hyperthyroid OR hyper-thyroid OR “Grave’s disease” OR “Graves disease” OR “Graves’ disease” OR “Hashimoto’s disease” OR “Hashimoto disease” OR “Hashimotos disease” OR “toxic multinodular goiter” OR “toxic nodular goiter” OR “toxic goiter” OR “toxic adenoma” OR “toxic thyroid nodule” OR “toxic nodule” OR thyroiditis OR thyrotoxicosis): title/abstract/keywords (word variations have been searched)

#2: (cancer OR tumor OR carcinoma OR neoplasm): title/abstract/keywords (word variations have been searched)

#3: (#1 AND #2)

#4: MeSH descriptor: [Cohort Studies] explode all trees

#5: MeSH descriptor: [Case-control Studies] explode all trees

#6: MeSH descriptor: [Observational Studies as Topic] explode all trees

#7: (#4 OR #5 OR #6)

#8 (#3 AND #7)

Results: 244 publications

Keywords in titles and abstracts

Pubmed

(((thyroid dysfunction*[Title/Abstract] OR thyroid disease*[Title/Abstract] OR thyroid disorder*[Title/Abstract] OR thyroid function*[Title/Abstract] OR thyroid hormone*[Title/Abstract] OR thyroid condition*[Title/Abstract] OR triiodothyronine[Title/Abstract] OR thyroxine[Title/Abstract] OR thyroid-stimulating hormone[Title/Abstract] OR TSH[Title/Abstract] OR hypothyroid[Title/Abstract] OR hypo-thyroid[Title/Abstract] OR hyperthyroid[Title/Abstract] OR hyper-thyroid[Title/Abstract] OR Grave's disease[Title/Abstract] OR Graves disease[Title/Abstract] OR Graves' disease[Title/Abstract] OR Hashimoto's disease[Title/Abstract] OR Hashimoto disease[Title/Abstract] OR Hashimotos disease[Title/Abstract] OR toxic multinodular goiter[Title/Abstract] OR toxic nodular goiter[Title/Abstract] OR toxic goiter[Title/Abstract] OR toxic adenoma[Title/Abstract] OR toxic thyroid nodule[Title/Abstract] OR toxic nodule[Title/Abstract] OR thyroiditis[Title/Abstract] OR thyrotoxicosis[Title/Abstract]) AND (cancer [Title/Abstract] OR cancers[Title/Abstract] OR tumor[Title/Abstract] OR tumors[Title/Abstract] OR tumour[Title/Abstract] OR tumours[Title/Abstract] OR carcinoma[Title/Abstract] OR carcinomas[Title/Abstract] OR neoplasm[Title/Abstract])) AND humans[MeSH Terms] AND (english[Language] OR french[Language] OR vietnamese[Language]) AND (cohort[Title/Abstract] OR case control[Title/Abstract] OR population study[Title/Abstract] OR prospective study[Title/Abstract] OR retrospective study[Title/Abstract] OR population-based[Title/Abstract] OR registry-linkage[Title/Abstract] OR register linkage[Title/Abstract])

Result: 960 publications

Cochrane

#1: (“thyroid dysfunction*” OR “thyroid disease*” OR “thyroid disorder*” OR “thyroid hormone*” OR “thyroid function*” OR “thyroid condition*” OR triiodothyronine OR thyroxine OR thyroid-stimulating hormone OR TSH OR hypothyroid OR hypo-thyroid OR hyperthyroid OR hyper-thyroid OR “Grave’s disease” OR “Graves disease” OR “Graves’ disease” OR “Hashimoto’s disease” OR “Hashimoto disease” OR “Hashimotos disease” OR “toxic multinodular goiter” OR “toxic nodular

goiter" OR "toxic goiter" OR "toxic adenoma" OR "toxic thyroid nodule" OR "toxic nodule" OR thyroiditis OR thyrotoxicosis): title/abstract/keywords (word variations have been searched)

#2: (cancer OR tumor OR carcinoma OR neoplasm): title/abstract/keywords (word variations have been searched)

#3: (#1 AND #2)

#4: (cohort OR "case control" OR "case-control" OR "population study" OR "prospective study" OR "population-based" OR "population based" OR "registry-linkage" OR "register linkage"): title/abstract/keywords (word variations have been searched)

#5: (#3 AND #4)

Result : 582 publications

Appendix 3. Modified Newcastle Ottawa scale

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE

CASE CONTROL STUDIES

(adapted on March 1, 2019)

Selection (x/4)

1) Is the case definition adequate?

a) Independent validation (i.e. incl. radiology/histology/anapath. confirmation) ✵

b) Record linkage (hospital/insurance data with no external validation, i.e. radiology/histology/ anapath.)

c) Self-report

d) No description

2) Representativeness of the cases

a) Consecutive or obviously representative series of cases, with exclusion/refusal rate <10%, or description provided of those excluded and no evidence of selection bias ✵

b) Potential for selection biases, or not stated

3) Selection of Controls

a) Community controls ✵

b) Hospital controls

c) No description

4) Definition of Controls

a) No history of disease (endpoint) ✵

b) Possible history of disease (endpoint), or not stated

Comparability (x/2)

1) Comparability of cases and controls on the basis of the design or analysis

a) Study controls for age, sex, calendar year (if overall study period ≥15 years), major site-specific factors, i.e. smoking for lung cancer; parity, 1st-degree family history, HRT/menopausal status for breast cancer; parity, oral contraception for ovarian cancer; 1st-degree family history, ethnicity for prostate cancer, and no evidence of difference in exposure-outcome times between cases and controls ✵

b) Study controls for any additional factor [e.g. ethnicity, socioeconomic/educational status, other family history of cancer, breastfeeding, other reproductive factors, alcohol consumption, diet, physical activity, body-mass index/obesity, diabetes, etc.] ✵

Exposure (x/5)

1) Ascertainment of exposure

a) Secure record (i.e. medical records incl. lab results/blood measures) where blind to case/control status (i.e. collected prior to disease occurrence) ✵

b) structured interview (prior to disease occurrence) or hospital/insurance data where blind to case/control status

c) Interview/other source not blinded to case/control status

d) written self-report

e) No description

2) Same method of ascertainment for cases and controls

a) Yes ✵

b) No, or not stated

3) Non-Response rate

a) Same rate for both groups, or overall rate <10% ✵

b) Non respondents described

c) Rate different and no designation, or not stated

4) Demonstration that exposure was prior to definition case/control status (not a consequence of outcome of interest)?

a) Yes, if exposure was ascertained >1 year after the date of case/control status ✵

b) No, if exposure may have been ascertained within the year before the date of case/control status, or not stated

5) Was exposure ascertained long enough before case/control selection to allow possibly related events to occur?

a) Yes, if mean/median time before date of case/control status ≥5 years ✵

b) No, if mean/median time before date of case/control status <5 years, or not stated

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE

COHORT STUDIES

(adapted on March 1, 2019)

Selection (x/4)

1) Representativeness of the exposed cohort

a) Truly representative of the general population ✸

b) Somewhat representative of the general population ✸

c) Selected group of users e.g. nurses, volunteers, hospitalized individuals, with specific health condition

d) No description of the derivation of the cohort

2) Selection of the non-exposed cohort

a) Drawn from the same community as the exposed cohort ✸

b) Drawn from a different source

c) No description of the derivation of the non-exposed cohort

3) Ascertainment of exposure

a) Secure record (i.e. medical records incl. lab results, or blood measures) ✸

b) Structured interview or hospital/insurance data with no external validation

c) Written self-report

d) No description

4) Demonstration that outcome of interest was not present at start of study/before ascertainment of exposure

a) Yes, if individuals with outcome of interest diagnosed/reported within the first year after study entry/ascertainment of exposure are excluded or considered as non-exposed ✸

b) No, otherwise

Comparability (x/2)

1) Comparability of cohorts on the basis of the design or analysis

a) Study controls for age, sex, follow-up time, calendar year (if overall study period ≥15 years), and major site-specific factors, i.e. smoking for lung cancer; parity, first-degree family history, HRT/menopausal status for breast cancer; parity, oral contraception (ovarian cancer); 1st-degree family history, ethnicity for prostate cancer; calendar year for thyroid cancer✸

b) Study controls for any additional factor (e.g. ethnicity, socioeconomic/educational status, other family history of cancer, breastfeeding, other reproductive factors, alcohol consumption, diet, physical activity, body-mass index/obesity, diabetes, etc.) ✸

Outcome (x/3)

1) Assessment of outcome

a) Independent blind (e.g. national/regional cancer registry) assessment (including radiology/histology/anapath. confirmation) ✵

b) Record linkage (hospital/insurance data with no external validation, i.e. radiology/histology/anapath.)

c) Self-report

d) No description

2) Was follow-up long enough for outcomes to occur

a) Yes, if mean/median follow-up time ≥5 years ✵

b) No, if mean/median follow-up time <5 years, or not stated

3) Adequacy of follow up of cohorts

a) Complete follow up - all subjects accounted for ✵

b) Subjects lost to follow up unlikely to introduce bias - small number lost - ≥ 90% follow up, or description provided of those lost, or linkage with national registry (emigration and linkage failure rate assumed to be <10%) ✵

c) Follow up rate <90% and no description of those lost, or suspicion that loss-of-follow-up is related to the outcome

d) No statement

Appendix 4. Overall risk of bias of 20 studies included in the systematic review

Table 1. Risk of bias categorization based on number of point

	Maximum number of point	High RoB	Moderate RoB	Low RoB
Selection	4	<2	2	>2
Comparability	2	0	1	2
Exposure (case-control studies)	5	<3	3	>3
Outcome (cohort studies)	3	<2	2	>2

Table 2. Overall risk of bias of 20 studies included in the systematic review

Case-control studies														
Study	**Selection**					**Comparability**			**Exposure**					
	S1	**S2**	**S3**	**S4**	**Overall rating**	**C1**	**C2**	**Overall rating**	**E1**	**E2**	**E3**	**E4**	**E5**	**Overall rating**
Talamini, 1997	A ❋	B	B	A ❋	Moderate risk	–	–	High risk	C	A ❋	A ❋	B	A* ❋	Moderate risk
Memon, 2002	A ❋	B	A ❋	A ❋	Low risk	–	–	High risk	C	A ❋	C	A ❋	A† ❋	Moderate risk
Cristofanilli, 2005	A ❋	A ❋	A ❋	A ❋	Low risk	A ❋	–	Moderate risk	B	A ❋	A ❋	B	A† ❋	Moderate risk
Welzel, 2007	A ❋	A ❋	A ❋	A ❋	Low risk	A ❋	–	Moderate risk	B	A ❋	A ❋	B	A* ❋	Moderate risk
Hassan, 2009	A ❋	A ❋	A ❋	A ❋	Low risk	A ❋	B ❋	Low risk	C	A ❋	A ❋	B	A† ❋	Moderate risk
Mondul, 2012	A ❋	B	A ❋	A ❋	Low risk	A ❋	B ❋	Low risk	A ❋	A ❋	A ❋	A ❋	B	Low risk
Huang, 2017	A ❋	A ❋	A ❋	A ❋	Low risk	A ❋	B ❋	Low risk	A ❋	A ❋	A ❋	B	B	Moderate risk
Petrick, 2017	A ❋	A ❋	A ❋	A ❋	Low risk	A ❋	–	Moderate risk	B	A ❋	A ❋	B	A* ❋	Moderate risk
Cohort studies														
Study	**Selection**					**Comparability**			**Outcome**					
	S1	**S2**	**S3**	**S4**	**Overall rating**	**C1**	**C2**	**Overall rating**	**O1**	**O2**	**O3**			**Overall rating**
Munoz, 1978	D	B	A ❋	B	High risk	–	–	High risk	D	A ❋	D			High risk
Goldman, 1988	C	B	A	A	Moderate risk	–	–	High risk	B	A	D			High risk

* Assumption based on the mean age and the age at Medicare initial enrollment period

† Assumption about self-reported medical chart/interviews on the patient history of thyroid cancer in the past, regional/national registries: the follow-up time was long enough to observe cancer incidence among participant

			❋	❋					❋				
Mellemgaard, 1998	C	A[‡] ❋	B	A ❋	Moderate risk	–	–	High risk	A ❋	A[†] ❋	B ❋		Low risk
Metso, 2007	C	B	A ❋	B	High risk	–	–	High risk	A ❋	A ❋	B ❋		Low risk
Hellevik, 2009	C	A ❋	A ❋	B[§]	Moderate risk	–[**]	–	High risk	A ❋	A ❋	B ❋		Low risk
Balasubramaniam, 2012	C	A ❋	B	A ❋	Moderate risk	A ❋	–	Moderate risk	B	A ❋	D		High risk
Chen, 2013a	A ❋	A ❋	B	B[§]	Moderate risk	–	–	High risk	A ❋	A[†] ❋	B ❋		Low risk
Chen, 2013b	A ❋	A ❋	B	B[§]	Moderate risk	–	–	High risk	A ❋	A[†] ❋	B ❋		Low risk
Kang, 2013	C	A ❋	C	B	High risk	A[††] ❋	B ❋	Low risk	C	A ❋	B ❋		Moderate risk
Yeh, 2013	B ❋	A ❋	B	B[§]	Moderate	A[‡‡] ❋	B ❋	Low risk	A ❋	B	B ❋		Moderate risk
Chan, 2017	C	A ❋	A ❋	A ❋	Low risk	A[§§] ❋	B[§§] ❋	Low risk	A ❋	A[†] ❋	B ❋		Low risk
Kitahara, 2018	A ❋	A[‡] ❋	B	A ❋	Low risk	A ❋	–	Moderate risk	A ❋	A ❋	B ❋		Low risk

[‡] The authors used the national incidence rate to compare with the study cohort, which was also from national registries. We considered that they were in a same source

[§] If the cancer of interest was breast or thyroid cancer for Chen, 2013a, colorectal or thyroid cancer for Chen, 2013b, prostate or lung cancer for Hellevik, 2009; thyroid cancer for Yeh, 2013, a point would be awarded to this item and the overall rating of Selection would be "low risk of bias"

[**] If the cancer of interest was lung cancer, a point would be awarded to this item and the overall rating of Comparability would be "moderate risk of bias"

[††] Not adjusted for calendar year but all other important factors

[‡‡] If the cancer of interest was respiratory tract cancer, the analysis was not adjusted for smoking but all other important factors

[§§] Not adjusted for calendar year but all other important factors for thyroid, breast and respiratory tract cancers. If the cancer of interest was prostate cancer, the analysis was not adjusted for ethnicity and 1st-degree family history of cancer, no point would be awarded to the two items of "Comparability"

Appendix 5. Thyroid dysfunction categorization based on thyroid hormone levels

TSH levels / FT4/FT3 levels	Below normal range	Above normal range
Above normal range		Overt hypothyroidism
Normal range	Subclinical hyperthyroidism	Subclinical hypothyroidism
Below normal range	Overt hyperthyroidism	

Appendix 6. Studies on the association between thyroid dysfunction and cancer mortality

Goldman MB, Maloof F, Monson RR, Aschengrau A, Cooper DS, Ridgway EC. Radioactive iodine therapy and breast cancer: a follow-up study of hyperthyroid women. American journal of epidemiology. 1988;127(5):969-80.

Goldman MB, Monson RR, Maloof F. Cancer mortality in women with thyroid disease. Cancer research. 1990;50(8):2283-9.

Goldman MB, Monson RR, Maloof F. Benign thyroid diseases and the risk of death from breast cancer. Oncology. 1992;49(6):461-6.

Hall P, Berg G, Bjelkengren G, Boice Jr JD, Ericsson UB, Hallquist A, et al. Cancer mortality after iodine-131 therapy for hyperthyroidism. International journal of cancer. 1992;50(6):886-90.

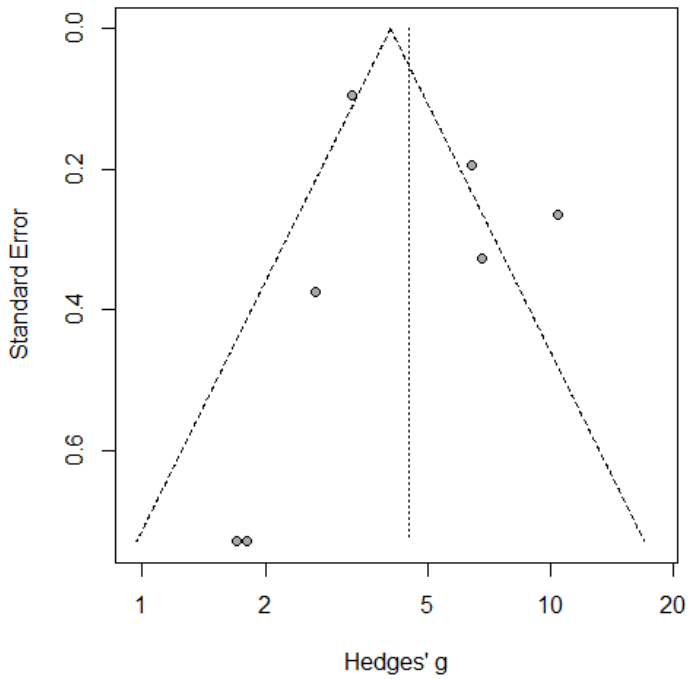
Hall P, Lundell G, Holm L-E. Mortality in patients treated for hyperthyroidism with iodine-131. European Journal of Endocrinology. 1993;128(3):230-4.

Journy NM, Bernier M-O, Doody MM, Alexander BH, Linet MS, Kitahara CM. Hyperthyroidism, hypothyroidism, and cause-specific mortality in a large cohort of women. Thyroid : official journal of the American Thyroid Association. 2017;27(8):1001-10.

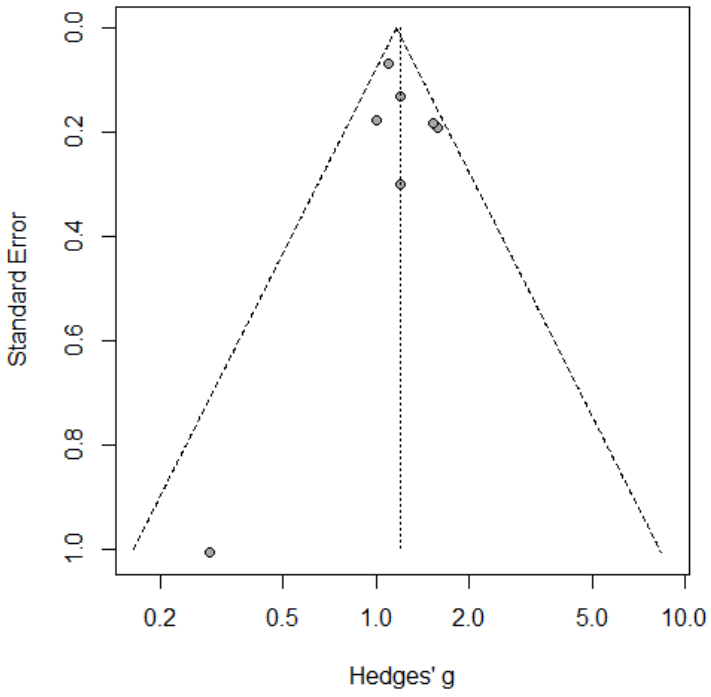
Metso S, Jaatinen P, Huhtala H, Auvinen A, Oksala H, Salmi J. Increased Cardiovascular and Cancer Mortality after Radioiodine Treatment for Hyperthyroidism. The Journal of Clinical Endocrinology & Metabolism. 2007;92(6):2190-6.

Ron E, Doody MM, Becker DV, Brill AB, Curtis RE, Goldman MB, et al. Cancer mortality following treatment for adult hyperthyroidism. Jama. 1998;280(4):347-55.

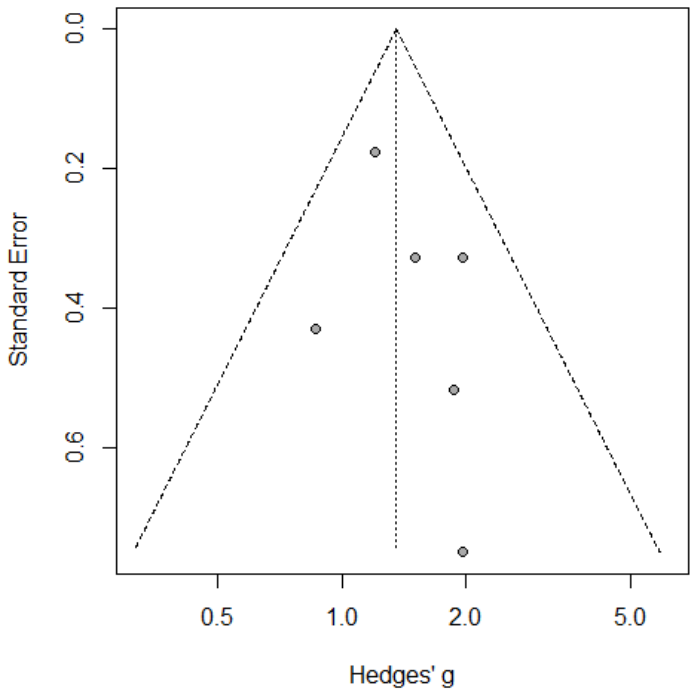
Tseng F-Y, Lin W-Y, Li C-I, Li T-C, Lin C-C, Huang K-C. Subclinical hypothyroidism is associated with increased risk for cancer mortality in adult Taiwanese—a 10 years population-based cohort. PloS one. 2015;10(4):e0122955.



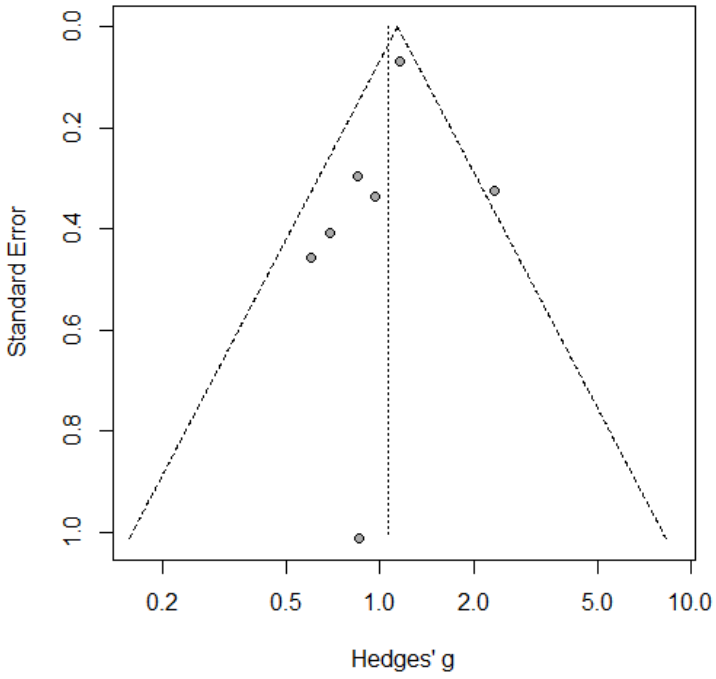
Supplementary Figure 1. Funnel plot for publication bias of the meta-analysis studying the association of hyperthyroidism and thyroid cancer risk. Egger test (p=0.65) revealed no evidence of publication bias



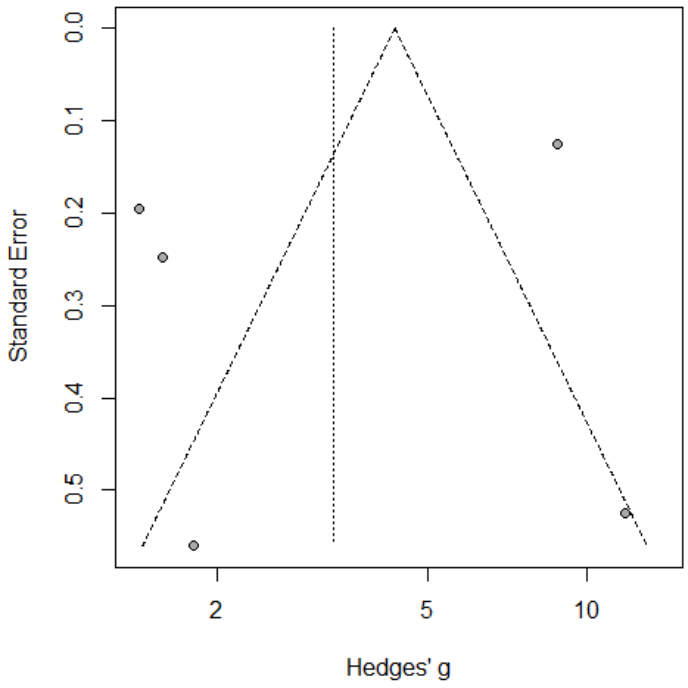
Supplementary Figure 2. Funnel plot for publication bias of the meta-analysis studying the association of hyperthyroidism and breast cancer risk. Egger test (p=0.85) revealed no evidence of publication bias



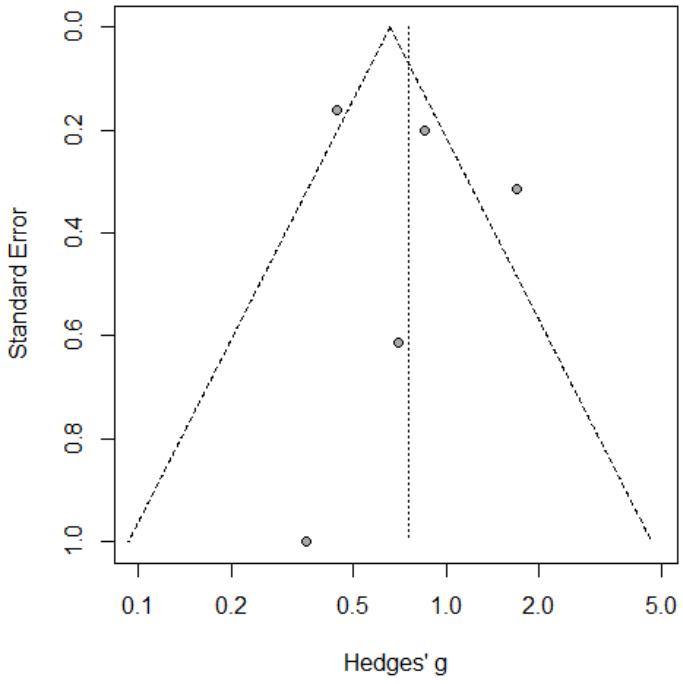
Supplementary Figure 3. Funnel plot for publication bias of the meta-analysis studying the association of hyperthyroidism and prostate cancer risk. Egger test (p=0.41) revealed no evidence of publication bias



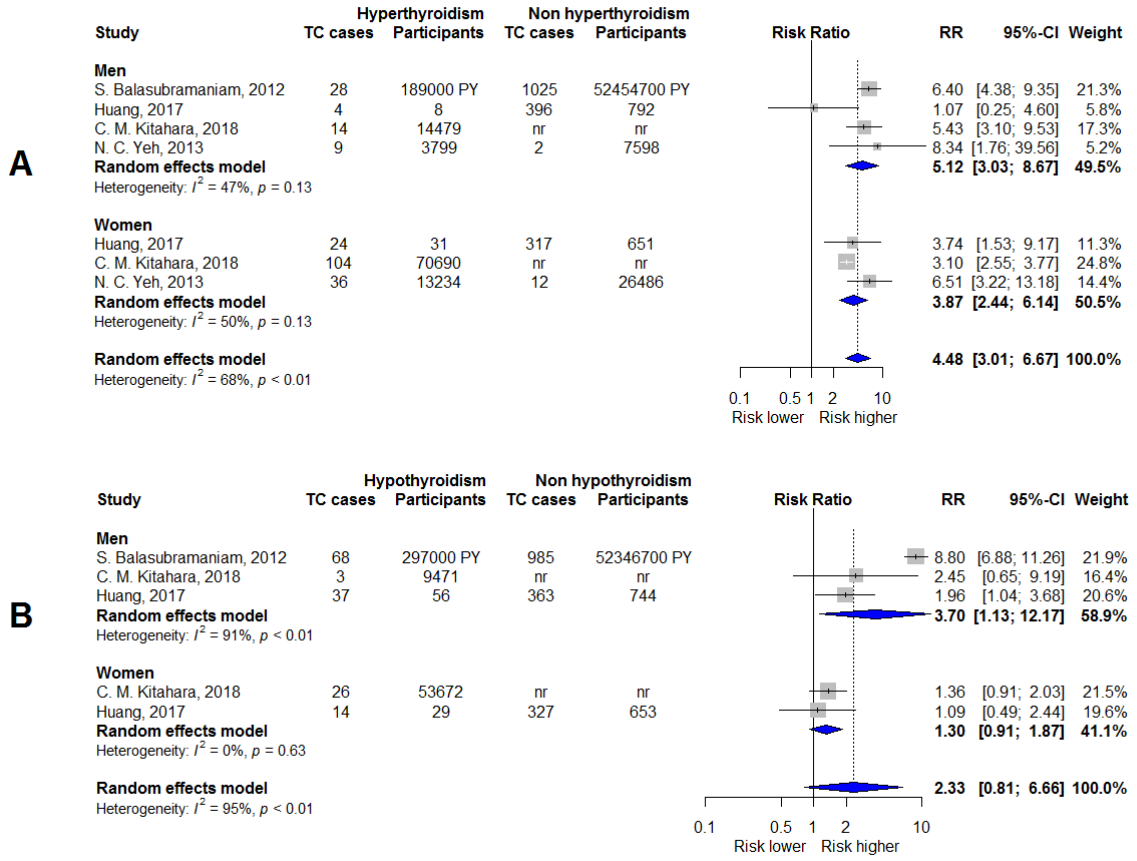
Supplementary Figure 4. Funnel plot for publication bias of the meta-analysis studying the association of hyperthyroidism and the risk of respiratory tract cancer. Egger test (p=0.49) revealed no evidence of publication bias



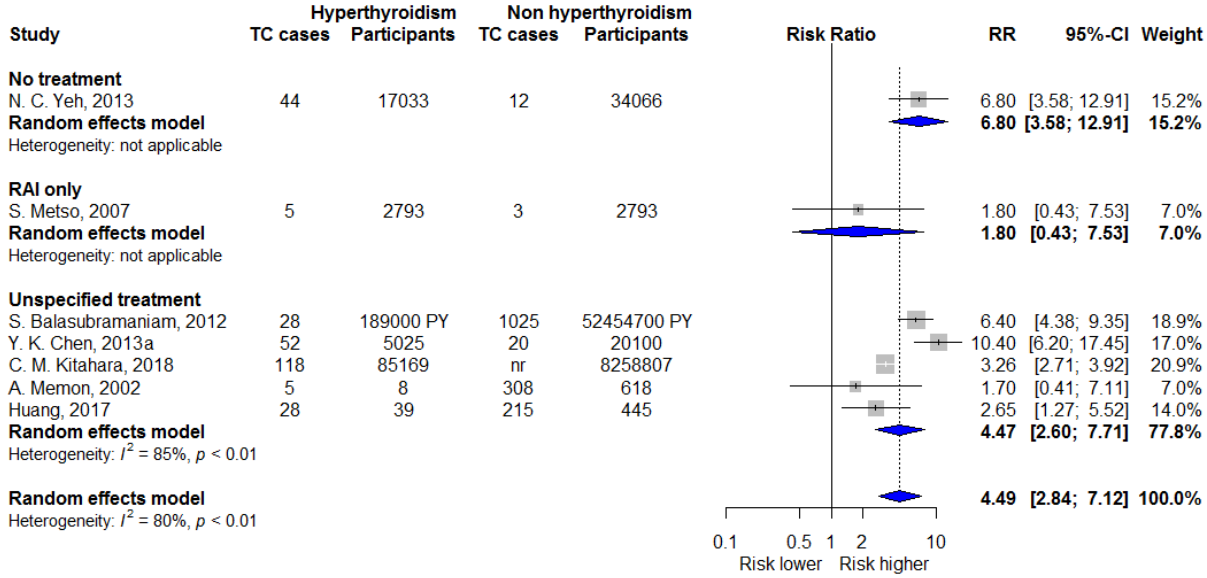
Supplementary Figure 5. Funnel plot for publication bias of the meta-analysis studying the association of hypothyroidism and thyroid cancer risk. Egger test (p=0.53) revealed no evidence of publication bias



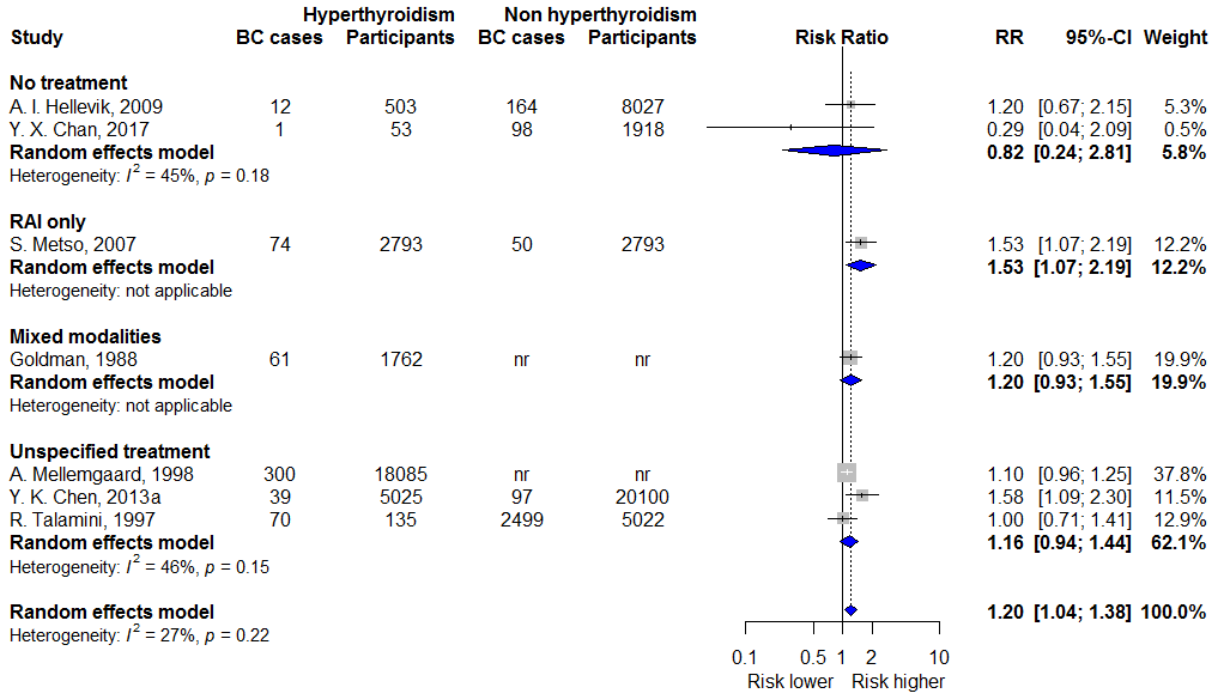
Supplementary Figure 6. Funnel plot for publication bias of the meta-analysis studying the association of hypothyroidism and breast cancer risk. Egger test (p=0.66) revealed no evidence of publication bias



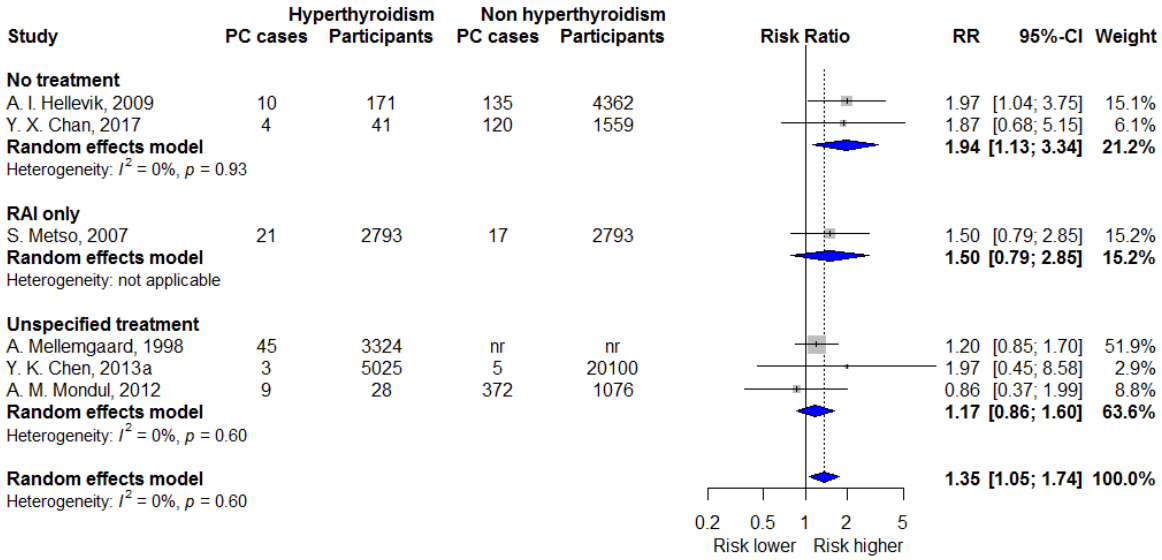
Supplementary Figure 7. Subgroup analysis by sex of the association between thyroid dysfunction and thyroid cancer risk. Relative risk, odds ratio, hazard ratio, and standardized incidence ratio were all considered as risk ratio. The test found no substantial difference between men and women. A. For hyperthyroidism analysis (p=0.43), B. For hypothyroidism analysis (p=0.10). Overall risk ratios are displayed as diamonds. The size of each square is proportional to the weight of the study. CI: Confidence interval, nr: Not reported, PY: person-year, RR: Risk ratio, TC: Thyroid cancer.



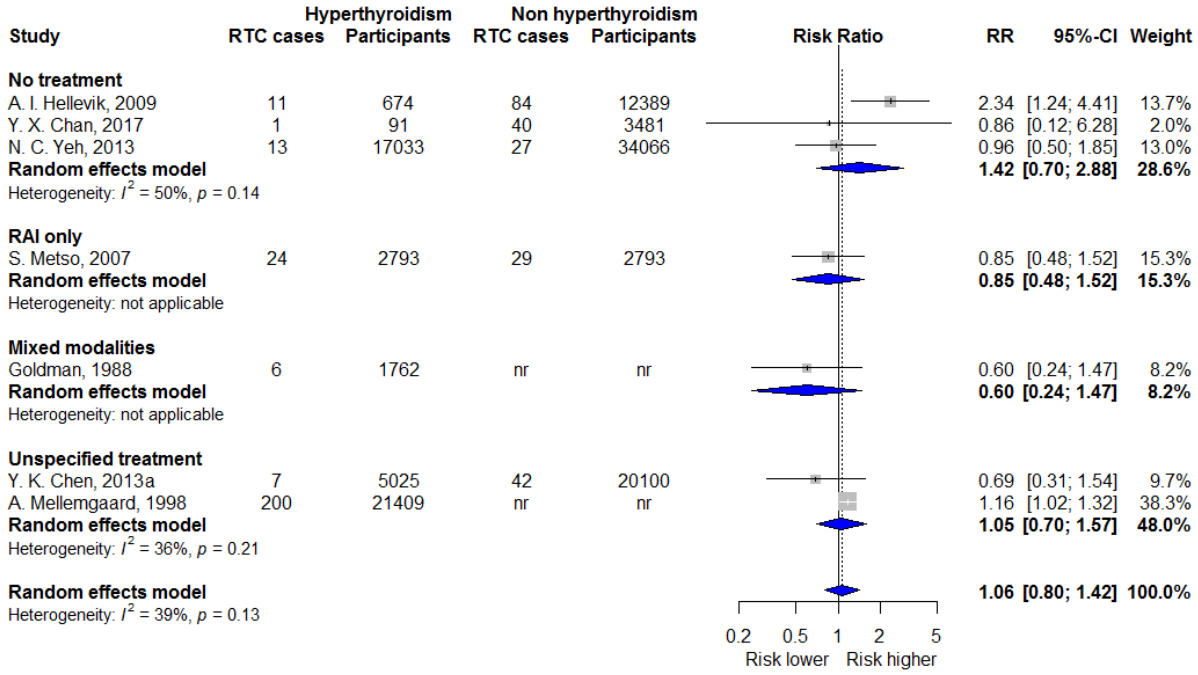
Supplementary Figure 8. Subgroup analysis by treatment methods of the association between hyperthyroidism and thyroid cancer risk. Relative risk, odds ratio, hazard ratio, and standardized incidence ratio were all considered as risk ratio. The test found no substantial difference among different treatment methods (p=0.22). Overall risk ratios are displayed as diamonds. The size of each square is proportional to the weight of the study. CI: Confidence interval, PY: person-year, RAI: Radioactive iodine, RR: Risk ratio, TC: Thyroid cancer.



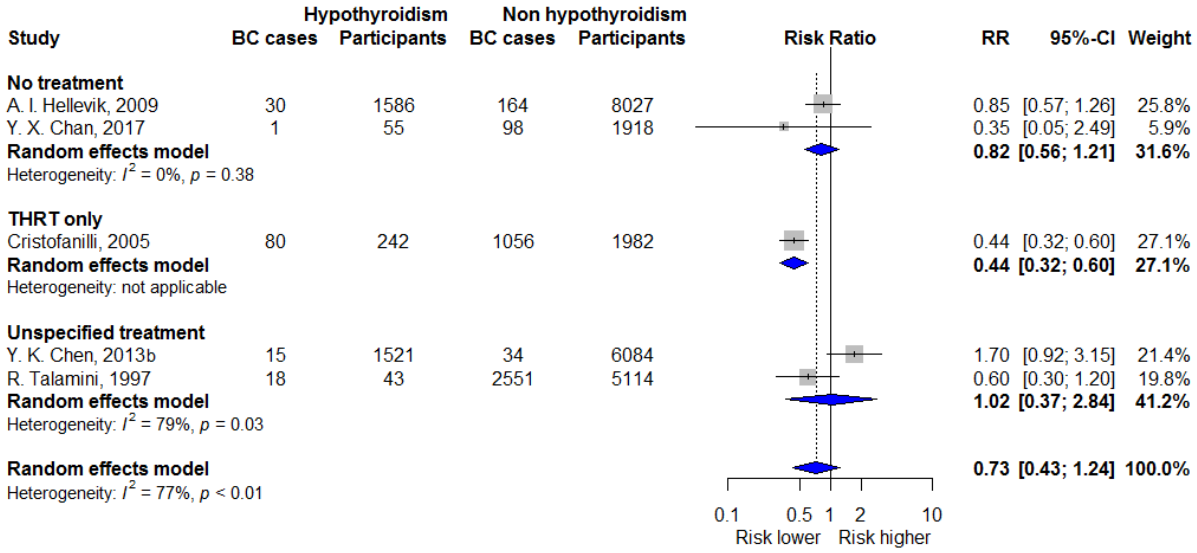
Supplementary Figure 9. Subgroup analysis by treatment methods of the association between hyperthyroidism and breast cancer risk. Relative risk, odds ratio, hazard ratio, and standardized incidence ratio were all considered as risk ratio. The test found no substantial difference among different treatment methods (p=0.54). Overall risk ratios are displayed as diamonds. The size of each square is proportional to the weight of the study. BC: Breast cancer, CI: confidence interval, nr: Not reported, PY: person-year, RAI: Radioactive iodine, RR: Risk ratio.



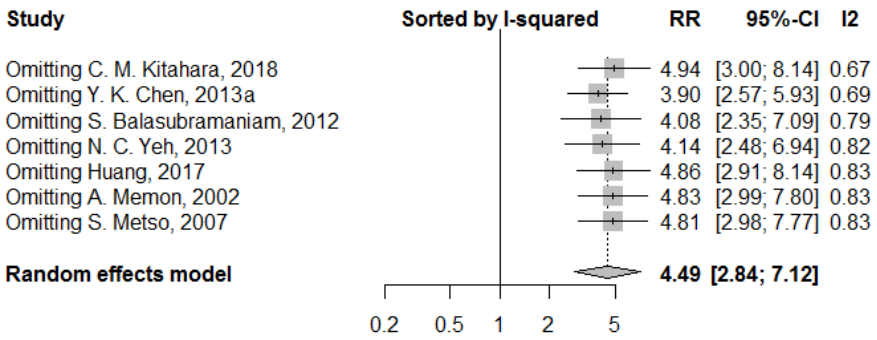
Supplementary Figure 10. Subgroup analysis by treatment methods of the association between hyperthyroidism and prostate cancer risk. Relative risk, odds ratio, hazard ratio, and standardized incidence ratio were all considered as risk ratio. The test found no substantial difference among different treatment methods (p=0.27). Overall risk ratios are displayed as diamonds. The size of each square is proportional to the weight of the study. CI: Confidence interval, nr: Not reported, PC: Prostate cancer, RAI: Radioactive iodine, RR: Risk ratio.



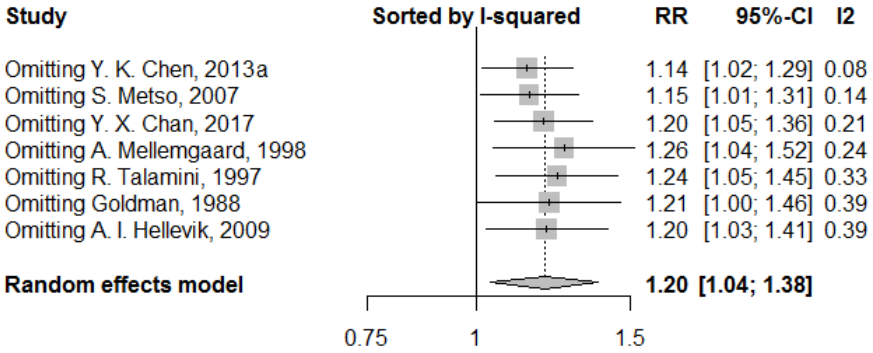
Supplementary Figure 11. Subgroup analysis by treatment methods of the association between hyperthyroidism and respiratory tract cancer risk. Relative risk, odds ratio, hazard ratio, and standardized incidence ratio were all considered as risk ratio. The test found no substantial difference among different treatment methods (p=0.47). Overall risk ratios are displayed as diamonds. The size of each square is proportional to the weight of the study. CI: Confidence interval, nr: Not reported, RAI: Radioactive iodine, RR: Risk ratio, RTC: Respiratory tract cancer.



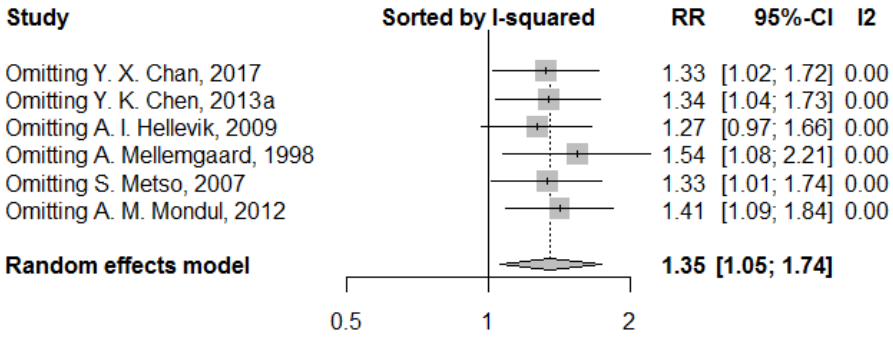
Supplementary Figure 12. Subgroup analysis by treatment methods of the association between hypothyroidism and breast cancer risk. Relative risk, odds ratio, hazard ratio, and standardized incidence ratio were all considered as risk ratio. The test found a statistically significant difference among different treatment methods (p=0.03). Overall risk ratios are displayed as diamonds. The size of each square is proportional to the weight of the study. CI: Confidence interval, BC: Breast cancer, RR: Risk ratio, THRT: Thyroid hormone replacement therapy.



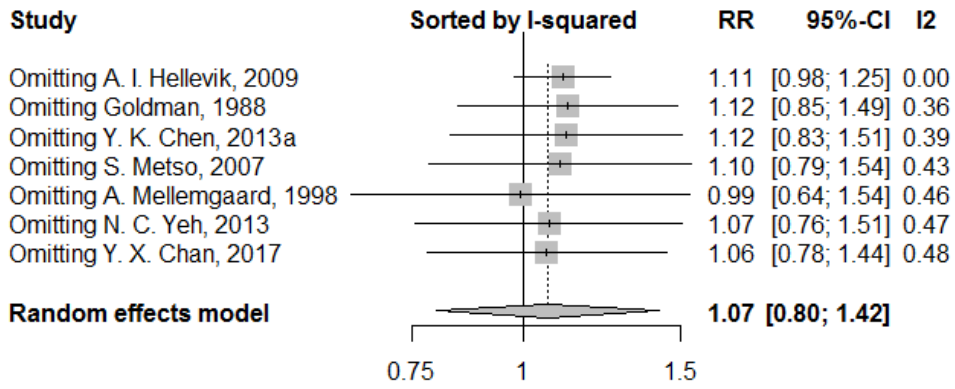
Supplementary Figure 13. Influence analysis of the association between hyperthyroidism and thyroid cancer risk



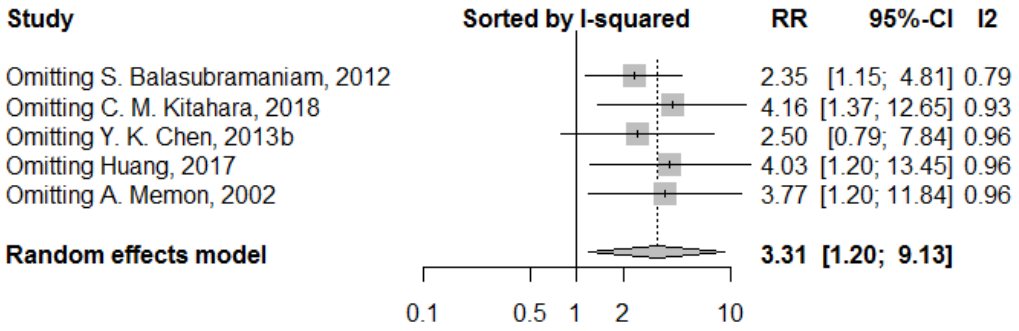
Supplementary Figure 14. Influence analysis of the association between hyperthyroidism and breast cancer risk



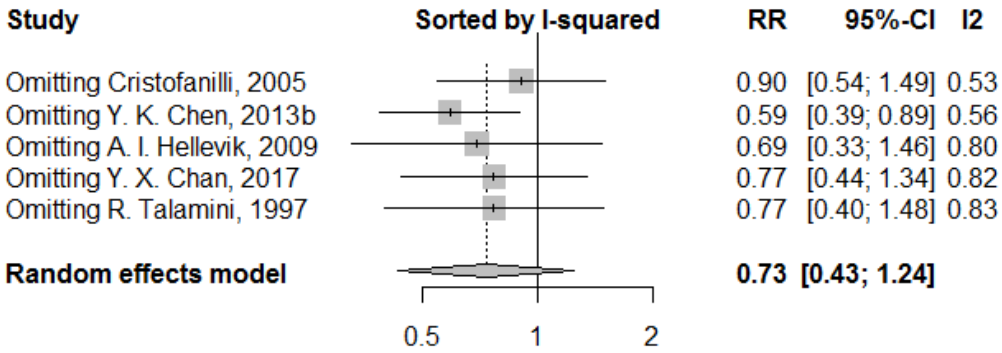
Supplementary Figure 15. Influence analysis of the association between hyperthyroidism and prostate cancer risk



Supplementary Figure 16. Influence analysis of the association between hyperthyroidism and respiratory tract cancer risk



Supplementary Figure 17. Influence analysis of the association between hypothyroidism and thyroid cancer risk



Supplementary Figure 18. Influence analysis of the association between hypothyroidism and breast cancer risk

Supplementary Table 1. Association between hyperthyroidism and the risk of different cancer sites other than thyroid, breast, prostate and respiratory tract cancer.

Cancer types	Study	Study design	Cases/Exposed	Cases/Non exposed	Results (95%CI)
Extrahepatic cholangiocarcinoma	Petrick, 2017	Case-control study	111/11751	2870/314845	aOR=0.99 (0.81-1.19)
	Welzel, 2007	Case-control study	30/3894	519/99437	aOR=1.7 (1.2-2.4)
Intrahepatic cholangiocarcinoma	Petrick, 2017	Case-control study	94/11734	1998/313973	aOR=1.25 (1.01-1.54)
	Welzel, 2007	Case-control study	27/3891	508/99426	aOR=1.5 (1.0-2.2)
Hepatoma cancer	Chen, 2013a	Cohort study	13/5025	42/20100	aHR=1.13 (0.60-2.12)
Hepatocellular carcinoma	Hassan, 2009	Case-control study	8/22	412/1502	aOR=1.7 (0.6-5.1)
Brain cancer	Goldman, 1988	Cohort study	5/1762	N/A	aSIR=2.3 (0.7-5.3)
	Mellemgaard, 1998	Cohort study	7/3324	N/A	aSIR=1.3 (0.5-2.6)
	Mellemgaard, 1998	Cohort study	44/18085	N/A	aSIR=1.5 (1.1-2.0)
	Metso, 2007*	Cohort study	7/2793	4/2793	aRR=1.9 (0.5-6.2)
Kidney cancer	Chen, 2013a	Cohort study	5/5025	18/20100	aHR=1.00 (0.37-2.72)
	Mellemgaard, 1998	Cohort study	10/3324	N/A	aSIR=1.1 (0.5-2.1)
	Mellemgaard, 1998	Cohort study	44/18085	N/A	aSIR=1.3 (1.0-1.8)
	Metso, 2007*	Cohort study	20/2793	9/2793	RR=2.32 (1.06-5.01)
Skin cancer	Mellemgaard, 1998	Cohort study	41/3324	N/A	aSIR=0.9 (0.6-1.2)
	Mellemgaard, 1998	Cohort study	168/18085	N/A	aSIR=0.8 (0.7-0.9)
	Metso, 2007*	Cohort study	24/2793	28/2793	aRR=0.9 (0.5-1.6)
Bladder cancer	Chen, 2013a	Cohort study	3/5025	14/20100	aHR=0.81 (0.23-2.84)
	Mellemgaard, 1998	Cohort study	26/3324	N/A	aSIR=0.9 (0.6-1.4)
	Mellemgaard, 1998	Cohort study	42/18085	N/A	aSIR=1.0 (0.8-1.4)
Ovarian Cancer	Chen, 2013a	Cohort study	0/5025	14/20100	-
	Kang, 2013	Cohort study	6/1010	1052/164670	aOR=0.67 (0.30-1.49)
Uterus cancer	Chen, 2013a	Cohort study	2/5025	15/ 20100	aHR=0.50 (0.11-2.19)
Endometrial cancer	Kang, 2013	Cohort study	15/1010	1176/164670	aOR=1.43 (0.85-2.39)
Cervical cancer	Chen, 2013a	Cohort study	3/5025	30/20100	aHR=0.45 (0.14-1.47)
Breast cancer	Munoz, 1978	Cohort study	4/342	N/A	SIR=0.8 (nr-nr)
Buccal cavity cancer	Mellemgaard, 1998	Cohort study	4/3324	N/A	aSIR=0.5 (0.1-1.3)
	Mellemgaard, 1998	Cohort study	20/18085	N/A	aSIR=1.3 (0.8-2.0)
Stomach cancer	Chen, 2013a	Cohort study	5/5025	21/20100	aHR=0.94 (0.35-2.51)
	Metso, 2007	Cohort study	30/2793	18/2793	aRR=1.75 (1.00-3.14)
Colon cancer	Chen, 2013a	Cohort study	9/5025	59/20100	aHR=0.61 (0.30-1.24)

	Hellevik, 2009	Cohort study	9/674	106/12389	aHR=1.38 (0.70-2.73)
Colorectal cancer	Chan, 2017	Cohort study	1/91	99/3481	aHR=0.38 (0.05-2.72)
Esophagus cancer	Metso, 2007*	Cohort study	5/2793	1/2793	aRR=5.1 (0.6-45)
Intestinal cancer	Metso, 2007*	Cohort study	44/2793	45/2793	aRR=1.0 (0.7-1.6)
Salivary glands cancer	Metso, 2007*	Cohort study	2/2793	0/2793	-
Hematopoietic cancer	Mellemgaard, 1998	Cohort study	17/3324	N/A	aSIR=0.9 (0.5-1.5)
	Mellemgaard, 1998	Cohort study	65/18085	N/A	aSIR=0.9 (0.7-1.2)
	Metso, 2007*	Cohort study	22/2793	18/2793	aRR=1.3 (0.7-2.4)
Hematologic cancer	Chen, 2013a	Cohort study	3/5025	25/20100	aHR=0.48 (0.14-1.59)
	Yeh, 2013	Cohort study	8/17033	14/34066	aHR=1.36 (0.59-3.16)
Pancreas cancer	Goldman, 1988	Cohort study	10/1762	N/A	aSIR=2.0 (1.0-3.7)

* Metso 2007: Results estimated based on a figure reported primary results of the article, exact results were not available.

Supplementary Table 2. Association between hypothyroidism and the risk of different cancer sites other than thyroid and breast cancer

Cancer types	Study	Study design	Cases/Exposed	Cases/Non exposed	Results (95% CI)
Prostate cancer	Chan, 2017	Cohort study	2/23	120/1559	aHR=0.81 (0.20-3.32)
	Chen, 2013b	Cohort study	1/1521	2/6084	aHR=2.89 (0.21-39.8)
	Hellevik, 2009	Cohort study	23/171	135/4362	aHR=0.86 (0.55-1.35)
	Mondul, 2012	Case-control study	20/95	372/1076	aOR=0.48 (0.28-0.81)
Hepatocellular carcinoma	Hassan, 2009	Case-control study	49/137	371/1387	aOR=1.9 (1.2-3.1)
Hepatoma cancer	Chen, 2013b	Cohort study	2/1521	11/6084	aHR=0.68 (0.15-3.08)
Ovarian cancer	Chen, 2013b	Cohort study	0/1521	1/6084	-
	Kang, 2013	Cohort study	92/12168	1052/164670	aOR=0.84 (0.68-1.04)
Bladder cancer	Chen, 2013b	Cohort study	0/1521	1/6084	-
Cervical cancer	Chen, 2013b	Cohort study	0/1522	5/6084	-
Endometrial cancer	Kang, 2013	Cohort study	123/12168	1176/164670	aOR=0.91 (0.75-1.10)
Uterus cancer	Chen, 2013b	Cohort study	1/1521	2/6084	aHR=2.00 (0.18-22.6)
Kidney cancer	Chen, 2013b	Cohort study	2/1521	3/6084	aHR=2.40 (0.38-15.1)
Colorectal cancer	Chan, 2017	Cohort study	3/77	99/3481	aHR=1.17 (0.37-3.72)
	Chen, 2013b	Cohort study	5/1521	5/6084	aHR=4.76 (1.36-16.6)
Colon cancer	Hellevik, 2009	Cohort study	23/2149	106/12389	aHR=0.95 (0.60-1.50)
Stomach cancer	Chen, 2013b	Cohort study	0/1521	6/6084	-
Thyroid lymphoma cancer	Chen, 2013b	Cohort study	1/1521	4/6084	aHR=0.94 (0.10-8.58)
Hematologic cancer	Chen, 2013b	Cohort study	2/1521	1/6084	aHR=7.95 (0.71-88.8)
Lung cancer	Chan, 2017	Cohort study	0/77	40/3481	-
	Chen, 2013b	Cohort study	0/1521	10/6084	-
	Hellevik, 2009	Cohort study	9/2149	84/12389	aHR=0.87 (0.43-1.74)

Supplementary Table 3. Subgroup and sensitivity analysis of the association between thyroid dysfunction and thyroid cancer risk

	Hyperthyroidism					Hypothyroidism				
	Studies, n	**Cases/Hyperthyroidism**	**Pooled RR (95%CI)**	**I2 %**	**p value**	**Studies, n**	**Cases/Hypothyroidism**	**Pooled RR (95%CI)**	**I2 %**	**p value**
Overall result from										
- Random effect	7	280	4.49 (2.84; 7.12)	80.0	<0.01	5	171	3.31 (1.20; 9.13)	95.4	<0.01
- Fixed effect	7	280	4.05 (3.49; 4.70)	80.0	<0.01	5	171	4.32 (3.60; 5.20)	95.4	<0.01
Ascertainment of hyperthyroidism					0.07					0.13
- Hospital-based data	5	247	5.36 (3.12; 9.21)	85.3	<0.01	3	111	5.10 (1.24; 20.94)	96.9	<0.01
- Other sources	2	33	2.42 (1.26; 4.64)	0	0.59	2	60	1.61 (1.04; 2.52)	0	0.83
Study design					0.07					0.13
- Cohort studies	5	247	5.36 (3.12; 9.21)	85.3	<0.01	3	111	5.10 (1.24; 20.94)	96.9	<0.01
- Case control studies	2	33	2.42 (1.26; 4.64)	0	0.59	2	60	1.61 (1.04; 2.52)	0	0.83
Geographic region					0.19					0.27
- Europe	2	123	3.23 (2.67; 3.89)	0	0.42	1	29	1.42 (0.95 - 2.04)	-	-
- US	2	56	4.37 (1.85; 10.28)	77.1	0.04	2	119	3.78 (0.70; 20.33)	97.4	<0.01
- Asia	3	101	6.35 (3.01; 13.39)	65.0	0.06	2	23	4.66 (0.74; 29.40)	83.3	0.01
Exclusion studies with high risk of bias in										
- Selection	6	275	4.81 (2.98; 7.77)	82.6	<0.01	5	171	3.31 (1.20; 9.13)	95.4	<0.01
- Comparability	4	218	4.42 (2.79; 7.00)	78.5	<0.01	3	148	2.73 (0.72; 10.30)	97.5	<0.01
- Exposure/Outcome	6	252	4.08 (2.35; 7.09)	78.7	<0.01	4	103	2.35 (1.15; 4.81)	79.4	<0.01
Min of follow-up=1 year	5	192	4.23 (2.82; 6.36)	65.7	0.02	4	120	2.78 (0.79; 9.84)	95.2	<0.01

Supplementary Table 4. Subgroup and sensitivity analysis of the association between thyroid dysfunction and breast cancer risk

	Hyperthyroidism					Hypothyroidism				
	Studies, n	**Cases/Hyperthyroidism**	**Pooled RR (95%CI)**	**I2 %**	**p value**	**Studies, n**	**Cases/Hypothyroidism**	**Pooled RR (95%CI)**	**I2 %**	**p value**
Overall result from										
- Random effect	7	557	1.20 (1.04; 1.38)	27.1	0.22	5	144	0.73 (0.43;1.24)	77.2	<0.01
- Fixed effect	7	557	1.16 (1.05; 1.29)	27.1	0.22	5	144	0.65 (0.52; 0.81)	77.2	<0.01
Ascertainment of hyperthyroidism					0.23					0.01
- Hospital-based data	4	474	1.26 (1.06; 1.49)	45.3	0.14	1	15	1.70 (0.92; 3.15)	-	-
- Other sources	3	83	1.02 (0.76; 1.37)	0	0.39	4	129	0.60 (0.37; 0.96)	56.7	0.07
Study design					0.28					0.02
- Cohort studies	6	487	1.24 (1.05; 1.45)	32.7	0.19	3	46	1.03 (0.55; 1.95)	56.6	0.10
- Case control studies	1	70	1.00 (0.70; 1.42)	-	-	2	98	0.46 (0.35; 0.62)	0	0.46
Geographic region					0.21					<0.01
- Europe	4	456	1.14 (0.99; 1.32)	12.6	0.33	2	48	0.78 (0.56; 1.10)	0	0.76
- US	1	61	1.20 (0.93; 1.54)	-	-	1	80	0.44 (0.32; 0.60)	-	-
- Asia	1	39	1.58 (1.09; 2.30)	-	-	1	15	1.70 (0.92; 3.15)	-	-
- Australia	1	1	0.29 (0.04; 2.10)	-	-	1	1	0.35 (0.05; 2.49)	-	-
Exclusion studies with high risk of bias in										
- Selection	6	483	1.15 (1.01; 1.31)	13.7	0.33	5	144	0.73 (0.43;1.24)	77.2	<0.01
- Comparability	1	1	0.29 (0.04; 2.10)	-	-	2	81	0.44 (0.32; 0.60)	0	0.82
- Exposure/Outcome	6	496	1.21 (1.00; 1.46)	38.8	0.15	5	144	0.73 (0.43;1.24)	77.2	<0.01
Min of follow-up=1 year	5	432	1.11 (1.00; 1.24)	0	0.52	1	1	0.35 (0.05; 2.53)	0	0.74

Supplementary Table 5. Subgroup and sensitivity analysis of the association between hyperthyroidism and prostate cancer risk

	Number of studies	Cases/Hyperthyroid participants	Pooled RR (95%CI)	I2 %	Q-statistic p value
Eligible study model					
- Random effects	6	92	1.35 (1.05; 1.74)	0	0.60
- Fixed effects	6	92	1.35 (1.05; 1.74)	0	0.60
Ascertainment of hyperthyroidism					0.61
- Hospital-based data	3	69	1.29 (0.95; 1.73)	0	0.71
- Other sources	3	23	1.51 (0.89; 2.55)	21.5	0.28
Study design					0.27
- Cohort studies	5	83	1.41 (1.09; 1.84)	0	0.66
- Case control studies	1	9	0.86 (0.37; 1.99)	-	-
Geographic region					0.70
- Europe	4	85	1.31 (1.01; 1.70)	0	0.40
- Asia	1	3	1.97 (0.45; 8.58)	-	-
- Australia	1	4	1.87 (0.68; 5.15)	-	-
After exclusion studies with high risk of bias in					
- Selection	5	71	1.33 (1.01; 1.75)	0	0.48
- Comparability	1	9	0.86 (0.37; 1.99)	-	-
- Exposure/Outcome	6	92	1.35 (1.05; 1.74)	0	0.6
Min of follow-up=1 year	4	68	1.47 (0.93; 2.32)	48.6	0.12

Supplementary Table 6. Subgroup and sensitivity analysis of the association between hyperthyroidism and the risk of respiratory tract cancer

	Number of studies	Cases/Hyperthyroid participants	Pooled RR (95%CI)	I2 %	Q-statistic p value
Eligible study model					
- Random effects	7	262	1.07 (0.80; 1.42)	38.6	0.13
- Fixed effects	7	262	1.14 (1.01; 1.29)	38.6	0.13
Type of cancer					0.81
- Lung cancer	3	19	1.23 (0.47; 3.18)	65.2	0.06
- Respiratory cancer	4	243	1.09 (0.92; 1.29)	5.3	0.37
Ascertainment of hyperthyroidism					0.03
- Hospital-based data	5	250	1.04（0.86; 1.27）	11.9	0.34
- Other sources	2	12	2.13 (1.17; 3.90)	0	0.35
Study design					-
- Cohort studies	7	262	1.07 (0.80; 1.42)	38.6	0.13
- Case control studies	0		-	-	-
Geographic region					0.41
- Europe	4	235	1.27 (0.82; 1.96)	65.4	0.06
- US	1	6	0.60 (0.24; 1.47)	-	-
- Asia	2	20	0.84 (0.51; 1.40)	0	0.53
- Australia	1	1	0.86 (0.12; 6.23)	-	-
After exclusion studies with high risk of bias in					
- Selection	6	238	1.10 (0.79; 1.54)	42.9	0.12
- Comparability (adjusted for smoking)	2	12	2.13 (1.17; 3.90)	0	0.35
- Exposure/Outcome	7	256	1.12 (0.85; 1.497)	36.1	0.17
Min of follow-up=1 year	5	217	1.27 (0.69; 2.35)	67.6	0.03

Received: 20 January 2021 | Revised: 5 April 2021 | Accepted: 29 April 2021

DOI: 10.1002/cam4.3978

Cancer Medicine Open Access WILEY

ORIGINAL RESEARCH

Thyroid dysfunction and breast cancer risk among women in the UK Biobank cohort

Thi-Van-Trinh Tran[1] | **Camille Maringe**[2] | **Sara Benitez Majano**[2] | **Bernard Rachet**[2] | **Marie-Christine Boutron-Ruault**[3] | **Neige Journy**[1]

[1]Epidemiology of radiation Group, Center for Research in Epidemiology and Population Health, INSERM U1018, Paris Sud-Paris Saclay University, Villejuif, France

[2]Inequalities in Cancer Outcomes Network, Department of Non-Communicable Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, UK

[3]Health across Generations Team, Center for Research in Epidemiology and Population Health, INSERM U1018, Paris Sud-Paris Saclay University, Villejuif, France

Correspondence
Thi-Van-Trinh TRAN, Gustave Roussy, INSERM U1018, Epidemiology of radiation, clinical epidemiology of cancer and survival Group, B2M, 39 rue Camille Desmoulins, 94800 Villejuif, France.
Email: Thivantrinh.TRAN@gustaveroussy.fr

Funding information
Thi-Van-Trinh TRAN received a doctoral grant from the Paris Sud-Paris Saclay University.

Abstract

This study aimed to evaluate the association between thyroid dysfunction and breast cancer risk. We included 239,436 females of the UK Biobank cohort. Information on thyroid dysfunction, personal and family medical history, medications, reproductive factors, lifestyle, and socioeconomic characteristics was retrieved from baseline self-reported data and hospital inpatient databases. Breast cancer diagnoses were identified through population-based registries. We computed Cox models to estimate hazard ratios (HRs) of breast cancer incidence for thyroid dysfunction diagnosis and treatments, and examined potential confounding and effect modification by comorbidities and breast cancer risk factors. In our study, 3,227 (1.3%) and 20,762 (8.7%) women had hyper- and hypothyroidism prior to the baseline. During a median follow-up of 7.1 years, 5,326 (2.2%) women developed breast cancer. Compared to no thyroid dysfunction, there was no association between hypothyroidism and breast cancer risk overall (HR = 0.93, 95% confidence interval (CI): 0.84–1.02, 442 cases), but we found a decreased risk more than 10 years after hypothyroidism diagnosis (HR=0.85, 95%CI 0.74–0.97, 226 cases). There was no association with hyperthyroidism overall (HR=1.08, 95%CI 0.86–1.35, 79 cases) but breast cancer risk was elevated among women with treated hyperthyroidism (HR=1.38, 95%CI: 1.03–1.86, 44 cases) or aged 60 years or more at hyperthyroidism diagnosis (HR=1.74, 95%CI: 1.01–3.00, 113 cases), and 5–10 years after hyperthyroidism diagnosis (HR=1.58, 95%CI: 1.06–2.33, 25 cases). In conclusion, breast cancer risk was reduced long after hypothyroidism diagnosis, but increased among women with treated hyperthyroidism. Future studies are needed to determine whether the higher breast cancer risk observed among treated hyperthyroidism could be explained by hyperthyroidism severity, type of treatment or aetiology.

KEYWORDS

breast cancer, cohort study, hyperthyroidism, hypothyroidism, incidence

1 | INTRODUCTION

Breast cancer is the most frequent female neoplasm, with 522,500 new cases diagnosed in Europe in 2018.[1] It has a peak incidence at the age of 50–70 years—a feature shared by thyroid dysfunction, one of the most common endocrine disorders in females. Experimental data showed that thyroxine (T4) and triiodothyronine (T3) have proliferative and anti-apoptotic effects on breast cancer tumour cells by regulating gene expression and stimulating oestrogen-like effects,[2,3] indicating an association between thyroid dysfunction and breast cancer risk.

However, epidemiological studies have provided inconsistent findings.[4] Several studies reported higher blood levels of thyroid stimulating hormone (TSH), a biomarker of hypothyroidism, to be associated with a reduced breast cancer risk,[5,6] while others reported no association.[7–9] In a meta-analysis of observational studies published up to 2019, no statistically significant association between hypothyroidism and breast cancer risk was found,[4] but two more recent studies reported a reduced breast cancer risk associated with hypothyroidism.[5,10] Conversely, some studies,[11–14] but not all,[8,10] showed a higher breast cancer risk among hyperthyroid women compared to those without thyroid dysfunction, which was supported by results from the meta-analysis [4] and a Mendelian randomization study.[5] This could be, at least partly, due to hyperthyroidism treatments, since radioactive iodine (RAI) therapy has been associated with an increased breast cancer risk,[13,15] but few studies had this information.

In this study, we aimed to estimate the association between hyper- and hypothyroidism (from self-report and medical records) and breast cancer risk among pre- and postmenopausal women, and investigated possible confounding or modifying effects of thyroid dysfunction treatment, comorbidities, and breast cancer risk factors, using data from the 2006–2010 cohort of the population-based UK Biobank (UKB) cohort.

2 | MATERIALS AND METHODS

2.1 | Study population and data sources

From 2006 to 2010, the UKB cohort enrolled 273,375 women from the general population. Participants were volunteers aged from 39 to 71 years, and residing in England, Wales, or Scotland, who gave their written informed consents.[16] Detailed information on personal and family medical history, medications, reproductive and lifestyle factors, and socioeconomic and demographic characteristics was collected through a self-reported questionnaire, an interview with a trained nurse, and physical measurements at baseline. The cohort was linked to regional, population-based registries to collect hospital inpatient diagnostics and procedures (data availability starting between 1981 and 1998 depending on the region), cancer registration (since 1957 to 1971 depending on the region), and death registration data (since 2006). Since the registries did not cover the participants' lives earlier than their availability date, we used those data sources for follow-up purposes, and both self-reported and registry-based data for baseline information (e.g. pre-existing cancer at baseline).

We included participants without cancer diagnosis of any type (except non-melanoma skin cancer) that was self-reported or recorded in cancer registries prior to baseline, i.e. the first visit at a UKB centre for study enrollment. We excluded women who underwent a mastectomy prior to baseline, or had less than one year of follow-up. After exclusions, our study population included 239,436 women (Figure 1). Follow-up time started at baseline and ended at the date of any cancer diagnosis (except non-melanoma skin cancer), mastectomy, death, lost-to-follow-up, or 31 March 2016, whichever occurred first.

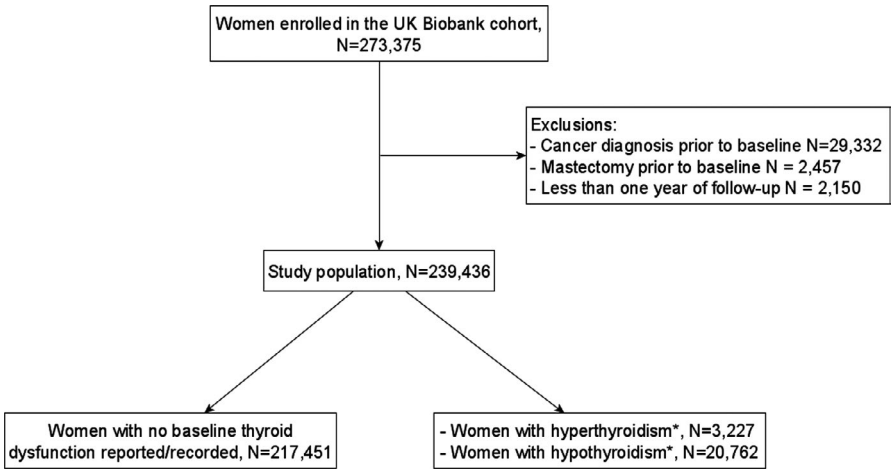


FIGURE 1 Flowchart of the study population. * Women with both hyper- and hypothyroidism reported/recorded (n = 2,004) contributed to both columns of hyper- and hypothyroidism

2.2 | Exposure

In the primary analyses, we used information on baseline thyroid dysfunction diagnosis (hyperthyroidism, hypothyroidism, no thyroid dysfunction reported/recorded) and treatments [hyperthyroidism: antithyroid drugs (ATDs) (carbimazole, propylthiouracil), RAI, thyroidectomy; hypothyroidism: thyroid hormones (liothyronine, thyroxine)] that was self-reported during the baseline interview or recorded (at least once) in a hospital inpatient database prior to baseline (Table 1, Appendix 1). Hyperthyroidism and hypothyroidism were assessed separately.

We investigated the following exposure variables: ever diagnosis of hyper-/hypothyroidism, thyroid dysfunction treatment modalities, time since diagnosis, time since treatment onset, age at diagnosis and calendar year of diagnosis.

2.3 | Outcome

Breast cancer cases were defined as diagnoses of invasive (n=4,452) or in situ cancers (n=874) recorded in the cancer registries (ICD-10: C50 or D05, ICD-9: 174 or 2330). We considered only first cancer occurrences. Women diagnosed with cancer of any type during follow-up (except non-melanoma skin cancer) were censored on diagnosis date.

2.4 | Potential confounders or effect modifiers

We considered comorbidities and breast cancer risk factors, and healthcare-related factors at baseline as potential confounders or effect modifiers (Appendix 2).

The comorbidities of interest were overweight/obesity, hypertension, diabetes, depression, and autoimmune conditions. Type 1 and 2 diabetes were identified using a modified version of a published algorithm that was developed using the UKB data and validated against external primary and secondary care databases (Appendix 3).[17] Since thyroid dysfunction aetiology was not systematically recorded in the UKB and various autoimmune conditions can occur among patients with thyroid autoimmune diseases such as Graves' or Hashimoto's disease,[18] we investigated a potential modifying effect by autoimmune conditions as a proxy for the autoimmune aetiology of thyroid dysfunction. We used a variable including any autoimmune condition other than autoimmune thyroid diseases at baseline (Appendix 4).[19–21]

We considered well-established breast cancer risk factors as potential confounders or effect modifiers: menopausal status, age at menarche, parity, age at first birth, family history of breast cancer, use of menopausal hormone therapy (MHT), use of oral contraception, and level of physical activities. Baseline age at menopause was defined as age at bilateral

TABLE 1 Sources of information and coding used to define thyroid dysfunction diagnosis and treatments

			Hospital inpatient databases			
		Self-reported data at baseline	ICD−9	ICD−10	OPCS−3	OPCS−4
Thyroid dysfunction diagnosis						
Hyperthyroidism		Graves' disease Hyperthyroidism Thyroid radioablation therapy Regular use of propilthiouracil or carbimazole at baseline	242	E05	988	X655
Hypothyroidism		Hypothyroidism Regular use of liothyronine or thyroxine at baseline	244, 2452	E02, E032-E039, E063, E089	NA	NA
Thyroid dysfunction treatment						
Hyperthyroidism treatment	Radioactive iodine[a]	Thyroid radioablation therapy	NA	NA	988	X655
	Surgery[a,b]	Thyroidectomy	NA	NA	070, 071, 072	B08
	Antithyroid drugs only[c]	Regular use of propilthiouracil or carbimazole at baseline	NA	NA		
Hypothyroidism treatment	Thyroid hormones	Regular use of liothyronine or thyroxine at baseline	NA	NA		

Abbreviations: ICD, International classification of diseases; NA, not applicableOPCS, OPCS Classification of Interventions and Procedures.

[a]Only the first definitive hyperthyroidism treatment was considered, e.g. if radioactive iodine occurred before surgery, the treatment modality was coded as "radioactive iodine".

[b]Only procedures performed after a diagnosis of hyperthyroidism were considered.

[c]If patients were treated with both antithyroid drugs and radioactive iodine/surgery, the treatment modality was coded as "radioactive iodine" or"surgery", whichever occurred first.

oophorectomy or reported menopause whichever occurred first. If unknown, it was defined in order of priority as age at MHT initiation, or 51 years otherwise. The age threshold corresponds to the median value of age at menopause in the study population.

Other factors suggested to be possibly associated with breast cancer risk in the literature were considered as potential confounders: race, alcohol consumption, and smoking status. Townsend deprivation score of residence, educational attainment, occupation, and adherence to breast and cervical cancer screening programs, which might reflect different levels of health care access and cancer surveillance, were also analysed as potential confounders.

For all the above-mentioned factors, missing data were infrequent (<5%, except age at menopause: 9.3%), and handled either by defining an "unknown" category (for categorical variables) or imputing the median value in the study population (for continuous variables).

2.5 | Statistical analyses

We used Cox proportional hazards models to compute hazards ratios (HRs) and 95% confidence intervals (CIs) of breast cancer incidence according to thyroid dysfunction diagnosis and treatments. Time since baseline (i.e. UKB inclusion) was considered as the time scale. Models were adjusted for age at baseline, menopausal status, family history of breast cancer, parity and age at first birth, and level of physical activity. Proportional hazards assumptions were graphically evaluated based on plots of scaled Schoenfeld residuals against time, and tested by introducing an interaction term between thyroid dysfunction and follow-up time. No evidence of non-proportionality was found.

Potential confounding effect was assessed by evaluating the age-adjusted associations with thyroid dysfunction, and changes in adjusted HRs for breast cancer risk exceeding 10%.[22] Effect modification was evaluated by testing the statistical significance of an interaction term between thyroid dysfunction and the studied covariate [likelihood-ratio χ^2 tests for heterogeneity (categorical variables) and linear trend (continuous variables)]. When statistically significant multiplicative interactions were detected, we reported results for both additive and multiplicative interactions.[23]

Several sensitivity analyses were conducted. While hyperthyroid patients are usually treated, the proportion of hyperthyroid women without information on treatment was too high to be considered as untreated individuals. Since ATDs are used as the first-line treatment for Graves' disease (the most common cause of hyperthyroidism) in the UK [24,25] and was more likely to be missed when retrieving information compared to surgery and RAI in the UKB, we hypothesized that women with no information on treatments were treated with ATDs, and conducted sensitivity analyses while combining them and women treated with ATDs. Thyroidectomy can be used to treat other thyroid diseases and thyroid dysfunction could be a transient condition before other thyroid disorders, therefore, we excluded women with other baseline thyroid problems, e.g. thyroiditis, and non-toxic goitre. To minimize misclassification, we conducted an analysis stratified by the order of thyroid dysfunction occurrence and excluded women who had hypothyroidism reported/recorded before hyperthyroidism or who had hyper- and hypothyroidism reported/recorded with unknown sequential order of occurrence. We also analysed separately thyroid dysfunction diagnoses and treatments recorded in the hospital databases only (likely reflecting the most severe conditions), and self-reported data only to assess the impact of the data sources on the results. We added information on new thyroid dysfunction diagnoses and hyperthyroidism treatment identified in the hospital databases during follow-up, by considering exposure as a time-dependent variable. We evaluated the association between thyroid dysfunction and invasive breast cancer risk only. We also computed cause-specific hazard models [26] to consider death and non-breast cancer incidence as competing risks. Lastly, we did a sensitivity analysis by excluding women with missing data in covariates.

3 | RESULTS

3.1 | Population description

The prevalence of hyper- and hypothyroidism at baseline was 1.3% and 8.7%, respectively. Compared to women with no thyroid dysfunction, hyper- and hypothyroid women were likely to be older, postmenopausal, MHT and oral contraception ever user, obese/overweight, to have had a child at an earlier age, to have a lower level of physical activity, and more comorbidities at baseline (Table 2, Table S1). During a median follow-up time of 7.1 years, 5326 (2.2%) women were diagnosed with breast cancer.

3.2 | Hyperthyroidism

We found no statistically significant association between breast cancer risk and hyperthyroidism in overall (Table 3), but an increased risk at 5–10 years after hyperthyroidism diagnosis (HR=2.38, 95% CI 1.19–4.76), among women who were diagnosed with hyperthyroidism after the age of 60 years (HR=1.74, 95% CI 1.01–3.00), or among women who were treated for hyperthyroidism (HR=1.38, 95% CI 1.03–1.86). Stratification by treatment status showed that the increase of risk among women who were diagnosed with hyperthyroidism for 5–10 years or at the age of 60 years or

TABLE 2 Baseline characteristics of the study population (n = 239,436)

	No thyroid dysfunction reported (n = 217,451)	Hyperthyroidism (n = 3,227)[a]		Hypothyroidism (n = 20,762)[a]	
			p-value[b]		*p* -value[b]
Person-years of follow-up, median (IQR)	7.1 (6.4, 7.8)	7.1 (6.4, 7.8)	0.377	7.0 (6.4, 7.8)	< 0.001
Age at baseline, Mean (SD)	56.4 ± 8.1	58.0 ± 7.6	<0.001	58.9 ± 7.3	<0.001
Menopause status, n (%)			<0.001		<0.001
Still had periods	60,047 (27.6)	612 (19.0)		3,189 (15.4)	
Had menopause before the age of 51	106,860 (49.1)	1,764 (54.7)		12,105 (58.3)	
Had menopause after the age of 51	50,544 (23.2)	851 (26.4)		5,468 (26.3)	
Age at menopause[c], Mean (SD)	49.3 ± 5.1	49.2 ± 5.4	0.918	49.0 ± 5.5	< 0.001
Age at menarche, Mean (SD)	13.0 ± 1.6	12.9 ± 1.6	0.213	12.9 ± 1.6	<0.001
Family history of breast cancer, n (%)	22,951 (10.6)	309 (9.6)	0.077	2,113 (10.2)	0.093
Ever use of menopausal hormone therapy[c], n (%)			<0.001		<0.001
No	77,660 (49.3)	1,193 (45.6)		7,473 (42.5)	
Yes, for less than 5 years	27,624 (17.5)	442 (16.9)		3,206 (18.2)	
Yes, for more than 5 years	41,604 (26.4)	764 (29.2)		5,384 (30.6)	
Yes, unknown duration	9,723 (6.2)	206 (7.9)		1,432 (8.1)	
Unknown	793 (0.5)	10 (0.4)		78 (0.4)	
Ever use of oral contraception, n (%)			<0.001		<0.001
No	39,784 (18.3)	723 (22.4)		4,722 (22.7)	
Yes, for less than 10 years	78,956 (36.3)	1,216 (37.7)		7,855 (37.8)	
Yes, for more than 10 years	78,019 (35.9)	972 (30.1)		6,070 (29.2)	
Yes, unknown duration	20,338 (9.4)	308 (9.5)		2,078 (10.0)	
Unknown	354 (0.2)	8 (0.2)		37 (0.2)	
Parity and age at first birth, n (%)			<0.001		<0.001
No live birth	41,026 (18.9)	567 (17.6)		3,336 (16.1)	
≥ one child, <30 years old at birth	135,291 (62.2)	2,134 (66.1)		14,340 (69.1)	
≥ one child, ≥30 years old at birth	40,071 (18.4)	516 (16.0)		3,007 (14.5)	
Unknown	1,063 (0.5)	10 (0.3)		79 (0.4)	
Corpulence, n (%)			0.024		<0.001
Obesity/Overweight, BMI ≥25 kg/m²	128,257 (59.0)	1,974 (61.2)		14,564 (70.1)	
Normal weight/Underweight, BMI <25 kg/m^2	88,047 (40.5)	1,239 (38.4)		6,107 (29.4)	
Unknown	1,147 (0.5)	14 (0.4)		91 (0.4)	
Comorbidities, n (%)			<0.001		<0.001
Type 2 diabetes	6,534 (3.0)	166 (5.1)		1,203 (5.8)	
Hypertension	49,848 (22.9)	1,006 (31.2)		6,579 (31.7)	
Depression	15,145 (7.0)	263 (8.1)		2,027 (9.8)	
Autoimmune diseases	20,263 (9.3)	450 (13.9)		2,851 (13.7)	
Levels of physical activities, n (%)			0.002		<0.001
Low	68,804 (31.6)	1,106 (34.3)		7,438 (35.8)	
Moderate	77,862 (35.8)	1,146 (35.5)		7,084 (34.1)	
High	70,785 (32.6)	975 (30.2)		6,240 (30.1)	

Abbreviation: BMI, Body-mass index

[a]Women with both hyper- and hypothyroidism reported/recorded (n=2,004) contributed to both columns of hyper- and hypothyroidism.

[b]*p*-value of t-test, Mann-Whitney U test and χ^2 test, where appropriate.

[c]Postmenopausal women only.

TABLE 3 Hazard ratios of breast cancer incidence associated to thyroid dysfunction diagnosis and treatment versus no thyroid dysfunction at baseline

	Hyperthyroidism			Hypothyroidism		
Characteristics	**No. of breast cancer cases/ Person-years**	**HR**	**95%CI**	**No. of breast cancer cases/ Person-years**	**HR**	**95%CI**
No thyroid dysfunction (reference)	4,854/1,518,670	**1**	**—**	4,854/1,518,670	1	—
Overall	79/22,520.6	1.08	0.86, 1.35	442/144,213.1	0.93	0.84, 1.02
Age at diagnosis						
Before 40 years old	20/8,436.4	0.75	0.48, 1.16	50/23,615.7	**0.71**	**0.54, 0.94**
Between 40–60 years old	45/11,725	1.18	0.88, 1.58	271/87,945.4	0.94	0.83, 1.06
After 60 years old	13/2,007.2	**1.74**	**1.01, 3.00**	70/16,728.3	1.11	0.88, 1.41
Unknown age at diagnosis	1/352	0.92	0.13, 6.56	51/15,923.6	0.97	0.73, 1.27
P-trend[a]			*0.145*			*0.452*
Time since diagnosis						
Less than 5 years ago	4/2,333.6	0.70	0.26, 1.87	34/15,154.9	0.91	0.65, 1.27
Between 5–10 years ago	25/4,947.4	**1.58**	**1.06, 2.33**	131/37,024.4	1.08	0.91, 1.29
More than 10 years ago	49/14,887.6	0.97	0.73, 1.29	226/76,110.1	**0.85**	**0.74, 0.97**
Unknown time at diagnosis	1/352	0.91	0.13, 6.47	51/15,923.6	0.99	0.75, 1.30
P-trend[a]			*0.124*			*0.872*
Calendar year at diagnosis						
Before 1990	26/6,910.3	1.09	0.74, 1.61	47/17,558.6	0.79	0.59, 1.05
1990–2000	14/5,946.9	0.74	0.44, 1.24	120/40,954.8	0.88	0.73, 1.05
After 2000	38/9,317.3	1.29	0.94, 1.77	224/69,814.3	0.99	0.86, 1.13
Unknown time at diagnosis	1/346.2	0.93	0.13, 6.60	51/15,885.4	0.96	0.73, 1.27
P-trend[a]			*0.366*			*0.352*
Treatment status						
Without information on treatment (1)	35/12,816.1	0.84	0.60, 1.17	22/4,831.6	1.39	0.91, 2.11
With information on treatment	44/9,704.5	**1.38**	**1.03, 1.86**	420/139,381.5	0.91	0.83, 1.01
Types of hyperthyroidism treatment						
Antithyroid medications (2)	9/1,978	1.46	0.76, 2.81			
RAI (3)	11/2,697.4	1.23	0.68, 2.23			
Surgery (4)	24/5,029.1	1.44	0.96, 2.15			
(1) or (2)	44/14,794.1	0.92	0.68, 1.24			
(3) or (4)	35/19,822.2	1.37	0.98,1.91			
Time since hyperthyroidism treatment						
Less than 5 years ago	1/435.2	0.97	0.14, 6.90			
Between 5–10 years ago	8/1,068.6	**2.38**	**1.19, 4.76**			
More than 10 years ago	26/6,192.9	1.24	0.84, 1.82			
Unknown time at diagnosis	9/2,007.8	1.43	0.74, 2.74			
P-trend[a]		*0.044*				

Note: HRs are adjusted for age at baseline (continuous), family history of breast cancer (yes/no), parity and number of live birth (No live birth/≥ one child, <30 years old at birth/≥ one child, ≥30 years old at birth/Unknown), menopausal status (premenopause/postmenopause before the age of 51/postmenopause after the age of 51), physical activities (Low/Moderate/High).

Abbreviations: HR, Hazard Ratio, CI, Confidence Interval, RAI, Radioactive iodine therapy.

[a]p-trend was calculated after excluding hyperthyroidism/hypothyroidism with unknown time at diagnosis/treatment.

more, only concerned treated individuals, while there was no association among women with no information on treatment (Table A3). The results did not substantially differ in sensitivity analyses (Tables S4, S6, Figure S1).

For treated hyperthyroidism, there was a higher breast cancer risk among women menopaused at ages >51 years (HR=2.07, 95% CI 1.33–3.22) compared to women who had earlier menopause (HR=1.18, 95% CI 0.76–1.83) or were premenopausal at baseline (HR=0.79, 95% CI 0.30–2.11) (p-heterogeneity=0.09) (Table 4). We found no confounding or modifying effect by comorbidities, and breast cancer risk factors, except hypertension based on very few cases (Figure S2).

3.3 | Hypothyroidism

We found no statistically significant association between hypothyroidism and breast cancer risk, overall (HR=0.93, 95% CI 0.84–1.02), or after stratification by calendar year at diagnosis or treatment (Table 3). However, there was a lower risk among women diagnosed with hypothyroidism before the age of 40 years (HR=0.71, 95% CI 0.54–0.94) or diagnosed for hypothyroidism for more than 10 years (HR=0.85, 95% CI 0.74–0.97). The results did not substantially differ in sensitivity analyses (Tables S5, S6 , Figure S1).

We found no confounding or modifying effect by comorbidities, and breast cancer risk factors (Figure S2), except age at menopause. We observed lower risks among premenopausal women at baseline (HR=0.69, 95% CI 0.51–0.93) or women menopaused at ages ≤ 51 years (HR=0.90, 95% CI 0.79–1.02) compared to those with later menopause (HR=1.10, 95% CI 0.93–1.30) (p-value for heterogeneity: 0.017) (Table 5). The results of analyses on age at menopause did not vary after adjustment for age at menopause (for postmenopausal women) and in further analyses stratified by age at baseline, natural or artificial menopause, age at or time since hypothyroidism diagnosis, occurrence of thyroid dysfunction before or after menopause, or use of MHT or not.

4 | DISCUSSION

In this study, there was no association between thyroid dysfunction and breast cancer risk overall. However, breast cancer risk varied according to hyperthyroidism treatment status, with a 38% higher breast cancer risk in women treated for hyperthyroidism compared to women with no thyroid dysfunction and no increased risk among hyperthyroid women without information on treatment. The risk was particularly elevated at 5–10 years after hyperthyroidism diagnosis and among women diagnosed for hyperthyroidism at the age of 60 years or more. Women with a history of hypothyroidism for 10 years or more or diagnosed before the age of 40 years were at a lower risk of breast cancer. Menopausal status and age at menopause modified the association of both treated hyper- and hypothyroidism.

Accumulated evidence in recent years has not provided a clear understanding of the role of hypothyroidism on breast cancer risk. Some [5,6,10] but not all studies [7-9] have suggested that higher blood levels of TSH and thyroid hormone replacement therapy were associated with a reduced risk of breast cancer. Our findings showed an inverse association between breast cancer risk and hypothyroidism among women

TABLE 4 Breast cancer risk associated with treated hyperthyroidism according to baseline menopausal status and age at menopause

Menopausal status and age at menopause	N with/without breast cancer	HR (95% CI)	HR (95% CI) within strata of menopausal status and age at menopause
Premenopause			
No thyroid dysfunction	1,194/58,853	1.19 (1.07–1.31), $p = 0.001$	1.00
Treated hyperthyroidism	4/248	0.91 (0.34–2.44), $p = 0.856$	0.77 (0.29–2.05), $p = 0.601$
Having menopause before the age of 51			
No thyroid dysfunction	2,341/104,519	1.00	1.00
Treated hyperthyroidism	20/743	1.19 (0.76–1.84), $p = 0.443$	1.19 (0.76–1.84), $p = 0.443$
Having menopause after the age of 51			
No thyroid dysfunction	1,319/49,225	1.16 (1.08–1.24), $p < 0.001$	1.00
Treated hyperthyroidism	20/358	2.39 (1.54–3.71), $p < 0.001$	2.07 (1.33–3.22), $p = 0.001$

Note: Measure of effect modification of premenopause on additive scale: Treated hyperthyroidism: RERI (95% CI) = −0.46 (−1.5–0.58), $p = 0.391$. Measure of effect modification of having menopause after the age of 51 on additive scale: Treated hyperthyroidism: RERI (95% CI) = 1.05 (−0.12–2.22), $p = 0.08$. Measure of effect modification of premenopause on multiplicative scale: Treated hyperthyroidism: ratio of HRs (95% CI) = 0.65 (0.22–1.9), $p = 0.429$. Measure of effect modification of having menopause after the age of 51 on multiplicative scale: Treated hyperthyroidism: ratio of HRs (95% CI) = 1.74 (0.93–3.25), $p = 0.081$. HRs are adjusted for age at baseline (continuous), family history of breast cancer (yes/no), parity and number of live birth (No live birth/≥ one child, <30 years old at birth/≥ one child, ≥30 years old at birth/Unknown), and physical activities (Low/Moderate/High).

diagnosed before 40 years of age or only after 10 years of hypothyroidism, in partial agreement with a previous meta-analysis and a recent study.[4,10]

In the current study, we reported an increased risk of breast cancer among women with treated hyperthyroidism while the meta-analysis [4] and two nationwide hospital cohort studies [11,12] suggested a higher risk with hyperthyroidism in general. Of note, in those studies, hyperthyroidism was mainly ascertained through hospital databases, thus, probably mostly including treated cases. One of the cohort studies [11] also had an older population compared to ours, which might partly explain the overall elevated risk with hyperthyroidism. In contrast, a recent cohort study did not find any association between self-reported hyperthyroidism and breast cancer risk, but information on treatment was limited and only available for medications.[10]

In our study, baseline characteristics did not differ substantially between hyperthyroidism with/without information on treatment (Table S2). Increased risk among hyperthyroid women with information on treatments, but not among those without information might be explained by surveillance bias, types of treatment themselves, or treatment-related factors. Women with treated hyperthyroidism could possibly have more regular health care consultations. However, the increased risk remained after 10 years of diagnosis and did not change after accounting for health care-related factors. Thus, surveillance bias was unlikely to be a major explanatory factor. Besides, hyperthyroid patients treated with RAI have been suggested to have a higher breast cancer risk, in relation to the radiation dose received. However, as the possible effect of RAI is modest and observed only after a long latency period,[13,15] it was unlikely the principal cause of the higher breast cancer risk among treated hyperthyroidism in our study. Moreover, we found consistent risks across different types of treatment, suggesting that breast cancer risk in treated hyperthyroidism was unlikely attributable solely to a specific treatment type.

Treatments are generally not recommended in subclinical hyperthyroidism when overt conditions are often treated as soon as diagnosed.[27] In the current study, hyperthyroid patients without information on treatment could have subclinical hyperthyroidism, which can be endogenous or exogenous (due to overtreated hypothyroidism), while patients with information on treatment might suffer from overt conditions. A recent large population-based linked-record study in the UK found that the majority (74%) of patients with Graves' disease were treated with ATDs.[25] Since the recommended length of an ATDs course often lasts no longer than 12–18 months, and in the UKB cohort, only ATDs which were regularly being taken at baseline were recorded, and not before, it is possible that hyperthyroid women without information on treatment were actually treated with ATDs, and we found no association with breast cancer risk among these patients in the sensitivity analysis including all those subjects as treated with ATDs. Nevertheless, we always observed higher breast cancer risks among hyperthyroidism treated with definitive treatments (RAI, surgery), which are preferred among patients with recurrent hyperthyroidism (likely having more severe manifestation [28]) or hyperthyroidism caused by toxic nodular goiter. Previous studies have suggested that the higher breast cancer

TABLE 5 Breast cancer risk associated with hypothyroidism according to baseline menopausal status and age at menopause

Menopausal status and age at menopause	N with/without breast cancer	HR (95% CI)	HR (95% CI) within strata of menopausal status and age at menopause
Premenopause			
No thyroid dysfunction	1194/58853	1.19 (1.08–1.32), $p = 0.001$	1.00
Hypothyroidism	44/3145	0.82 (0.61–1.12), $p = 0.214$	0.69 (0.51–0.93), $p = 0.016$
Having menopause before the age of 51			
No thyroid dysfunction	2341/104519	1.00	1.00
Hypothyroidism	240/11865	0.90 (0.79–1.02), $p = 0.109$	0.90 (0.79–1.02), $p = 0.109$
Having menopause after the age of 51			
No thyroid dysfunction	1319/49225	1.15 (1.08–1.24), $p < 0.001$	1.00
Hypothyroidism	158/5310	1.27 (1.08–1.49), $p = 0.004$	1.10 (0.93–1.30), $p = 0.261$

Note: Measure of effect modification of premenopause on additive scale: Hypothyroidism: RERI (95% CI) = −0.26 (−0.55–0.02), $p = 0.066$. Measure of effect modification of having menopause after the age of 51 on additive scale: Hypothyroidism: RERI (95% CI) = 0.22 (−0.02–0.46), $p = 0.073$. Measure of effect modification of premenopause on multiplicative scale: Hypothyroidism: ratio of HRs (95% CI) = 0.77 (0.55–1.07), $p = 0.121$. Measure of effect modification of having menopause after the age of 51 on multiplicative scale: Hypothyroidism: ratio of HRs (95% CI) = 1.23 (0.99–1.51), $p = 0.06$. HRs are adjusted for age at baseline (continuous), family history of breast cancer (yes/no), parity and number of live birth (No live birth/≥ one child, <30 years old at birth/≥ one child, ≥30 years old at birth/Unknown), and physical activities (Low/Moderate/High).

risk associated with hyperthyroidism was strongest among patients with toxic nodular goiters.[12,29] In our study, breast cancer risk did not vary when stratifying by the presence of autoimmune disease. Thus, the aetiology of thyroid dysfunction might not be related to the increased risk.

Most,[6,7,9,30] but not all,[8] previous studies found breast cancer risk increased with increasing blood levels of thyroxine (a marker of hyperthyroidism severity). A recent study which included women without thyroid medication found that both abnormal high blood levels of thyroxine and thyroxine in the euthyroid range were associated with higher breast cancer risk, but the risk associated with overt hyperthyroidism was higher than that with subclinical conditions.[6]

Biological mechanisms underlying the association between breast cancer risk and TSH remains unclear, but a number of explanation for thyroid hormones have been explored in vitro and in vivo. T4 and T3 activate MPAK pathways and phosphorylate ER α, inducing cell proliferation.[2,3,31] T3 can also enhance the effect of oestrogens on breast cell proliferation,[32] and directly increases aerobic glycolysis, a hallmark of cancer, which is known as Warburg effect.[2] T4 is known to have anti-apoptotic properties, which act via the integrin α vβ3, by stimulating gene expression of cancer cell defense.[33,34] Moreover, excessive or insufficient iodine intake, which plays a key role in thyroid hormone production, could also be a risk factor for breast cancer.[35] Taken together, current experimental evidence supports a positive association between high levels of thyroid hormones and a higher risk of breast cancer.

In this study, the breast cancer risk estimates for thyroid dysfunction were not affected by a wide range of potential confounders and effect modifiers, except menopausal status and late age at menopause irrespective of other factors. Few studies have investigated a potential effect modification by menopausal status and reproductive factors. A recent study showed a positive association between hyperthyroidism and reproductive risk factors of breast cancer.[12] In a large cohort of postmenopausal women, the reduced risk of breast cancer associated with hypothyroidism disappeared among women who used MHT for any duration.[10] Some other studies found evidence of a stronger association with high levels of T4 among postmenopausal women compared to premenopausal ones.[6,7,30] Among postmenopausal women, the association between T4 and breast cancer risk was also stronger among obese women,[30] who had higher oestrogen blood concentration than women with normal weight.[36] Taken together, the current evidence suggested that reproductive factors might modify the breast cancer risk associated with thyroid dysfunction.

Late age at menopause has been confirmed risk factor of breast cancer, which lengthens the cumulative exposure to cycling reproductive hormones among women.[37] After menopause, endogenous oestrogen is produced dominantly by the peripheral conversion of androgens in adipose tissue,[36] which is represented by BMI. Almost 40%–50% variation in natural age at menopause has been suggested to be attributable to genetic factors.[38,39] However, in our study, the association between breast cancer and thyroid dysfunction did not vary according to other genetic- and oestrogen-related factors. Besides, although the proportion of ER + and ER- breast cancer has been shown to vary according to age at breast cancer diagnosis among both pre- and postmenopausal women,[37] we observed no substantial difference in the distribution of age at breast cancer diagnosis according to thyroid dysfunction and menopausal status. Thus, the underlying biological mechanisms of the effect modification by menopausal status and age at menopause remain unclear.

The current study has major strengths, including a large population size, a high level of follow-up completeness and outcome ascertainment through regional registries and hospital databases, and its wide range of available information. The crossover among inpatient data and self-reported data on personal medical history allowed us to capture a broad range of health conditions. The UKB also includes detailed information on reproductive factors, lifestyle, socioeconomic status and family medical history with low levels of missing data, which helped us to study essential risk factors.

However, several limitations can be flagged. Details on cancer stage, grade, and receptor status were unavailable, and we could not investigate whether the risk estimates varied according to tumour characteristics. Lack of information on laboratory measurements of thyroid hormones, aetiology, and clinical symptoms of thyroid dysfunction prevented us from determining the severity, the exposure window of thyroid dysfunction (as overt conditions are often treated as soon as diagnosed) and disentangling the independent role of severity, and aetiology. We were unable to account for thyroid dysfunction diagnosis/treatments for the whole study population during follow-up or to study the independent effects of thyroid dysfunction treatments, and evaluate the impact of different treatment-related factors: RAI dosage, partial versus total thyroidectomy, duration of use and adherence to ATDs prescription. In the hyperthyroidism analyses, given that the higher risks were consistent across different types of treatment, accounting for treatment-related factors is unlikely to change our risk estimates. However, considering the intertwined relationship between hyperthyroidism aetiology, severity and treatment for further research is needed to confirm our finding. The data on comorbidities were also quite limited with no information on severity, age at onset, and duration of conditions, so it is possible that we did not account for all the possible effects of comorbidities on the association between thyroid dysfunction and breast cancer risk.

In conclusion, our study suggested that higher breast cancer risk among hyperthyroid women could be explained by hyperthyroidism severity or aetiology, while there was a

lower risk among women with 10 years or more of hypothyroidism. The association between thyroid dysfunction and breast cancer risk was modified by menopausal status and age at menopause, suggesting that the positive association between increased blood levels of thyroid hormones and breast cancer risk was even stronger with late age at menopause.

ACKNOWLEDGEMENTS

The authors would like to thank Dr Cari M Kitahara for valuable discussions.

CONFLICT OF INTERESTS

The authors declare no conflict of interest.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was performed under generic ethical approval obtained by UK Biobank from the National Health Service National Research Ethics Service (approval letter ref 16/NW/0274, 13 May 2016).

DATA AVAILABILITY STATEMENT

This work has been conducted using the UK Biobank Resource under Application Number 35032. Bona-fide researchers can apply to use the UK Biobank dataset by registering and applying at http://www.ukbiobank.ac.uk/register-apply.

ORCID

Thi-Van-Trinh Tran https://orcid.org/0000-0003-3132-9055

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018;68(6):394-424.
2. Goemann IM, Romitti M, Meyer ELS, Wajner SM, Maia AL. Role of thyroid hormones in the neoplastic process: an overview. *Endocr Relat Cancer*. 2017;24(11):R367-R385.
3. Krashin E, Piekiełko-Witkowska A, Ellis M, Ashur-Fabian O. Thyroid hormones and cancer: a comprehensive review of preclinical and clinical studies. *Front Endocrinol*. 2019;10:59.
4. Tran TV, Kitahara CM, de Vathaire F, Boutron-Ruault MC, Journy N. Thyroid dysfunction and cancer incidence: a systematic review and meta-analysis. *Endocr Relat Cancer*. 2020;27(4):245-259.
5. Yuan S, Kar S, Vithayathil M, et al. Causal associations of thyroid function and dysfunction with overall, breast and thyroid cancer: A two-sample Mendelian randomization study. *Int J Cancer*. 2020;147(7):1895-1903.
6. Kim EY, Chang Y, Lee KH, et al. Serum concentration of thyroid hormones in abnormal and euthyroid ranges and breast cancer risk: A cohort study. *Int J Cancer*. 2019;145(12):3257-3266.
7. Tosovic A, Becker C, Bondeson AG, et al. Prospectively measured thyroid hormones and thyroid peroxidase antibodies in relation to breast cancer risk. *Int J Cancer*. 2012;131(9):2126-2133.
8. Hellevik AI, Asvold BO, Bjøro T, Romundstad PR, Nilsen TI, Vatten LJ. Thyroid function and cancer risk: a prospective population study. *Cancer Epidemiol Biomarkers Prev*. 2009;18(2):570-574.
9. Khan SR, Chaker L, Ruiter R, et al. Thyroid function and cancer risk: the rotterdam study. *J Clin Endocrinol Metabol*. 2016;101(12):5030-5036.
10. Weng CH, Okawa ER, Roberts MB, et al. Breast cancer risk in postmenopausal women with medical history of thyroid disorder in the women's health initiative. *Thyroid*. 2020;30(4):519-530.
11. Søgaard M, Farkas DK, Ehrenstein V, Jørgensen JO, Dekkers OM, Sørensen HT. Hypothyroidism and hyperthyroidism and breast cancer risk: a nationwide cohort study. *Eur J Endocrinol*. 2016;174(4):409-414.
12. Yang H, Holowko N, Grassmann F, Eriksson M, Hall P, Czene K. Hyperthyroidism is associated with breast cancer risk and mammographic and genetic risk predictors. *BMC Med*. 2020;18(1):225.
13. Metso S, Auvinen A, Huhtala H, Salmi J, Oksala H, Jaatinen P. Increased cancer incidence after radioiodine treatment for hyperthyroidism. *Cancer*. 2007;109(10):1972-1979.
14. Chen YK, Lin CL, Chang YJ, et al. Cancer risk in patients with Graves' disease: a nationwide cohort study. *Thyroid*. 2013;23(7):879-884.
15. Kitahara CM, Berrington de Gonzalez A, Bouville A, et al. Association of radioactive iodine treatment with cancer mortality in patients with hyperthyroidism. *JAMA Int Med*. 2019;179(8):1034-1042.
16. Sudlow C, Gallacher J, Allen N, et al. UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. *PLoS Med*. 2015;12(3):e1001779.
17. Eastwood SV, Mathur R, Atkinson M, et al. Algorithms for the capture and adjudication of prevalent and incident diabetes in UK Biobank. *PLoS One*. 2016;11(9):e0162388.
18. Antonelli A, Benvenga S. Editorial: The association of other autoimmune diseases in patients with thyroid autoimmunity. *Front Endocrinol*. 2018;9:540.
19. Schairer C, Pfeiffer RM, Gadalla SM. Autoimmune diseases and breast cancer risk by tumor hormone-receptor status among elderly women. *Int J Cancer*. 2018;142(6):1202-1208.
20. Thomas SL, Griffiths C, Smeeth L, Rooney C, Hall AJ. Burden of mortality associated with autoimmune diseases among females in the United Kingdom. *Am J Public Health*. 2010;100(11):2279-2287.
21. Eaton WW, Pedersen MG, Atladóttir HO, Gregory PE, Rose NR, Mortensen PB. The prevalence of 30 ICD-10 autoimmune diseases in Denmark. *Immunol Res*. 2010;47(1–3):228-231.
22. Maldonado G, Greenland S. Simulation study of confounder-selection strategies. *Am J Epidemiology*. 1993;138(11):923-936.
23. Knol MJ, VanderWeele TJ. Recommendations for presenting analyses of effect modification and interaction. *Int J Epidemiol*. 2012;41(2):514-520.
24. Vaidya B, Williams GR, Abraham P, Pearce SH. Radioiodine treatment for benign thyroid disorders: results of a nationwide survey of UK endocrinologists. *Clin Endocrinol*. 2008;68(5):814-820.
25. Okosieme OE, Taylor PN, Evans C, et al. Primary therapy of Graves' disease and cardiovascular morbidity and mortality: a linked-record cohort study. *Lancet Diabetes Endocrinol*. 2019;7(4):278-287.
26. Putter H, Fiocco M, Geskus RB. Tutorial in biostatistics: competing risks and multi-state models. *Statistics in Med*. 2007;26(11):2389-2430.

27. Kahaly GJ, Bartalena L, Hegedüs L, Leenhardt L, Poppe K, Pearce SH. 2018 European thyroid association guideline for the management of graves' hyperthyroidism. *Eur Thyroid J*. 2018;7(4):167-186.
28. De Leo S, Lee SY, Braverman LE. Hyperthyroidism. *Lancet*. 2016;388(10047):906-918.
29. Ron E, Doody MM, Becker DV, et al. Cancer mortality following treatment for adult hyperthyroidism. *JAMA*. 1998;280(4):347-355.
30. Ortega-Olvera C, Ulloa-Aguirre A, Ángeles-Llerenas A, et al. Thyroid hormones and breast cancer association according to menopausal status and body mass index. *Breast Cancer Res*. 2018;20(1):94.
31. Tang HY, Lin HY, Zhang S, Davis FB, Davis PJ. Thyroid hormone causes mitogen-activated protein kinase-dependent phosphorylation of the nuclear estrogen receptor. *Endocrinology*. 2004;145(7):3265-3272.
32. Hall LC, Salazar EP, Kane SR, Liu N. Effects of thyroid hormones on human breast cancer cell proliferation. *J Steroid Biochem Mol Biol*. 2008;109(1–2):57-66.
33. Lin HY, Chin YT, Shih YJ, et al. In tumor cells, thyroid hormone analogues non-immunologically regulate PD-L1 and PD-1 accumulation that is anti-apoptotic. *Oncotarget*. 2018;9(75):34033-34037.
34. Davis PJ, Goglia F, Leonard JL. Nongenomic actions of thyroid hormone. *Nature reviews Endocrinology*. 2016;12(2):111-121.
35. Dong L, Lu J, Zhao B, Wang W, Zhao Y. Review of the possible association between thyroid and breast carcinoma. *World journal of surgical oncology*. 2018;16(1):130.
36. Cleary MP, Grossmann ME. Minireview: Obesity and breast cancer: the estrogen connection. *Endocrinology*. 2009;150(6):2537-2542.
37. Collaborative Group on Hormonal Factors in Breast Cancer. Menarche, menopause, and breast cancer risk: individual participant meta-analysis, including 118 964 women with breast cancer from 117 epidemiological studies. *Lancet Oncol*. 2012;13(11):1141-1151.
38. Morris DH, Jones ME, Schoemaker MJ, Ashworth A, Swerdlow AJ. Familial concordance for age at natural menopause: results from the Breakthrough Generations Study. *Menopause*. 2011;18(9):956-961.
39. Murabito JM, Yang Q, Fox C, Wilson PW, Cupples LA. Heritability of age at natural menopause in the Framingham Heart Study. *J Clin Endocrinol Metab*. 2005;90(6):3427-3430.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Tran T-V, Maringe C, Benitez Majano S, Rachet B, Boutron-Ruault M-C, Journy N. Thyroid dysfunction and breast cancer risk among women in the UK Biobank cohort. *Cancer Med*. 2021;10:4604–4614. https://doi.org/10.1002/cam4.3978

Breast cancer risk among thyroid cancer survivors and the role of I-131 treatment

Short title: Breast cancer risk in thyroid cancer survivors

Thi-Van-Trinh Tran[1,2,3]; Carole Rubino[1,2,3], Rodrigue Allodji[1,2,3], Milena Andruccioli[4], Stéphane Bardet[5], Carine Corone[6†], Ibrahima Diallo[1,2,3], Massimo Dottorini[7], Per Hall[8,9], Michel Henry-Amar[10], Stephanie Lamart[11], Françoise Le Thai[12], Stefan Lönn[13], Marcel Ricard[14], Claire Schvartz [15], Martin Schlumberger[16], Neige Journy[1,2,3]; Florent de Vathaire[1,2,3]

Affiliations:

1 Radiation Epidemiology Team, U1018 INSERM, Center for Research in Epidemiology and Population Health (CESP), F-94805 Villejuif Cedex

2 Department of Research, Gustave Roussy, F-94805 Villejuif Cedex

3 University Paris Saclay University, Gustave Roussy, Villejuif, France

4 Department of Nuclear Medicine, Sant'Anna Hospital, via Napoleona 60, 22100 – Como, Italy

5 Department of Nuclear Medicine and Thyroid Unit, Centre François Baclesse, Caen, France. s.bardet@baclesse.fr

6 Department of Nuclear Medicine, Rene Huguenin Cancer Research Center, 35 rue Dailly, 92210 Saint-Cloud, France. † Deceased

7 Department of Diagnostic Imaging, Nuclear Medicine Unit, Perugia General Hospital, Perugia, Italy. massimo.dottorini@ospedale.perugia.it

8 Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, 171 65 Stockholm, Sweden. per.hall@ki.se

9 Department of Oncology, Södersjukhuset, 118 83 Stockholm, Sweden

10 Centre de Traitement des Données du Cancéropôle Nord-Ouest, Plateforme de Recherche Clinique Ligue Contre le Cancer, Centre François Baclesse, 3 Avenue Général Harris, 14076, Caen, Cedex 5, France. m.henry.amar@baclesse.unicancer.fr

11 Laboratoire d'Évaluation de la Dose Interne, Institut de Radioprotection et de Sûreté Nucléaire, IRSN/PSE-SANTE/SDOS/LEDI, 31 avenue de la Division Leclerc, 92260 Fontenay-aux-Roses, France. stephanie.lamart@irsn.fr

12 Institut Curie Saint-Cloud, 92210 Saint-Cloud, France

13 Department of Research and Development, Region Halland, Halmstad, Sweden. Stefan.Lonn@regionhalland.se

14 Department of Physics, Gustave Roussy and Paris Saclay University, Villejuif, France Marcel.RICARD@gustaveroussy.fr

15 Nuclear medicine-thyroid Unit, Institut Godinot, 1, rue du Général-Koenig, 51100 Reims, France; Thyroid Cancer Registry of Marne-Ardennes, Institut Godinot, 1, rue du Général-Koenig, 51100 Reims, France claire.schvartz@reims.unicancer.fr

16 Department of Nuclear Medicine and Endocrine Oncology, Gustave Roussy and University Paris-Saclay, 94800 Villejuif, France Martin.SCHLUMBERGER@gustaveroussy.fr

Corresponding author: Carole Rubino, Gustave Roussy, INSERM U1018, Cancer and Radiation Group, B2M, 39 rue Camille Desmoulins, 94800 Villejuif, France

Telephone: (+33) 142 11 55 73

Email address: Carole.rubino@gustaveroussy.fr

Keywords: Second breast cancer, thyroid cancer, radioactive iodine, pooled analysis

Word count: 3,412 words

Abbreviations: CI, confidence interval; ERR, excess relative risk; EAR, excess absolute risk; IPW: Inverse probability weighting, NIS, sodium-iodine symporter; RR, relative risk; SIR, standardized risk ratio

Abstract (351 words)

Background: The risk of breast cancer following thyroid cancer diagnosis is of a great concern but still debated. In this study, we estimated the subsequent risk of breast cancer among women with a primary thyroid cancer and investigated the potential role of I-131 treatment.

Methods: We pooled individual data of three cohorts including women who were treated for differentiated thyroid cancer in 1934-2005 in France, Italy, and Sweden, and survived 2 years without malignancy after their first cancer diagnosis. Patient information including treatment modalities (surgery, external radiotherapy, I-131 treatment) was obtained using hospital-based medical records. Subsequent breast cancer was identified through medical records and/or national registries. We estimated standardized incidence ratios (SIRs) to compare breast cancer rates in female thyroid cancer survivors with those of the general population in each country. We investigated breast cancer risk in relation to cumulative I-131 activities and incidental doses to the breast using time-dependent analyses and considering a minimal latency time of 10 years between I-131 treatment and breast cancer incidence.

Results: Of 8,475 women (mean age at diagnosis: 45 years, range 2-90 years), 335 were diagnosed for breast cancer (SIR=1.52, 95% confidence interval (CI): 1.36-1.69) during a median follow-up time of 12.7 years (range 2-67 years) since diagnosis. Overall, the risk of breast cancer did not differ between women treated or not with I-131 [relative risk (RR) = 1.07 (95% CI 0.84-1.35), absolute excess risk (AER) = 0.8 per 10,000 person-years, 95%CI -4.9-6.4]. However, breast cancer risk increased linearly with increasing cumulative I-131 activity (excess relative risk per 100 mCi=17%, 95% CI: 2% to 38%, p_{trend}=0.028). There was a 2.41-fold (95%CI 1.13-4.52) increased risk in women who received a cumulative activity of ≥400 mCi, compared to non-I-131 treated women, which translated into 42 I-131-related breast cancer cases in excess per 10,000 person-years.

Conclusions: In this study, thyroid cancer survivors had a slightly higher risk of breast cancer compared to the general population. Overall, I-131 treatment did not increase breast cancer risk, but women who received a cumulative activity of ≥400 mCi had an increased risk of breast cancer compared to women without I-131 treatment

Introduction

Thyroid cancer is the most common endocrine cancer, with 67,817 new cases estimated in 2020 in Europe (1) and an increasing observed incidence over the last decades, particularly among women (2, 3). Most cases are papillary and follicular thyroid cancers, peaking at the age of 45-54 (2, 3). Treatment for thyroid cancer consists of thyroidectomy with or without a single administration of I-131 to ablate remnants and repeated administrations of I-131 in case of distant metastases. This protocol has been greatly successful with a 10-year overall survival exceeding 90% (4). With a long life expectancy, a major concern is thus long-term adverse outcomes, including a 1.25-fold higher rate of developing breast cancer compared to the general population (5). This increase cannot be explained by surveillance bias alone (5-7). There is a need of identifying factors that contribute to the increased risk of breast cancer among thyroid cancer survivors.

As breast is one of the most radiosensitive organs (8), I-131 treatment could be a factor constituting the elevated risk of breast cancer after a thyroid cancer diagnosis, along with genetic susceptibility, or shared hormonal and environmental factors (6, 9). Although ecological data from the Chernobyl radiation accident previously suggested such an association with internal radiation exposure (10, 11), results on the exposure to medical I-131 treatment have been conflicting. Some studies reported a higher risk of breast cancer among I-131-treated thyroid cancer survivors (9, 12) while others showed no association or even a lower risk compared to non I-131-treated patients (13, 14). In addition, the limited number of cases and follow-up time in some studies (12, 15, 16), the lack of a non I-131-treated comparison group (17) and the unavailability of details on I-131 activities in some others (17-

19) also hamper the interpretation of the association between I-131 treatment and breast cancer risk among thyroid cancer survivors (14).

In a pooled analysis of three large cohorts in Europe, we previously reported a higher breast cancer risk among thyroid cancer survivors compared to the general population (20). The present paper aimed to update results on breast cancer incidence in these cohorts with new patients included and a longer follow-up, and to evaluate the dose-response relationship with cumulative I-131 activities, as well as the corresponding estimated absorbed doses to the breast.

Methods

Population

We combined data of three European cohorts for patients with histologically confirmed papillary or follicular thyroid cancer diagnosis as the first primary cancer. These cohorts have been described in detail elsewhere (20-23). Briefly, the Swedish cohort included patients treated for thyroid cancer between 1950 and 1983 in six university hospitals. The Italian cohort consists of patients diagnosed with or treated for thyroid cancer from 1958 to 1996 at the nuclear medicine department of the General Hospital in Busto Arsizio, Italy. The French cohort included patients treated for thyroid cancer from 1934 to 2005 in four hospitals. Compared to the previous pooled analysis (20), the current study included 2,202 and 92 new patients from the French and Italian cohorts, respectively, who were initially treated during the period 1995-2005. We extended the follow-up time up to 7, 11, and 20 years for the Swedish, Italian, and French cohorts, respectively.

120 We excluded patients with external radiotherapy prior to thyroid cancer diagnosis (n=80), any
121 malignancy in the two years after thyroid cancer diagnosis (n=273), less than two years of
122 follow-up (n=543) or who were diagnosed at the age of 95 or more (n=1). Finally, our study
123 population included 8,475 women (Figure 1).

124 We retrieved information on thyroid cancer diagnosis, treatment modalities (surgery, external
125 radiotherapy, and internal radiotherapy with I-131), internal and external radiotherapy
126 administration date and their administered activities from medical records of each cancer
127 center. Invasive subsequent cancer cases and deaths were ascertained with medical records
128 in the French and Italian cohorts, and retrieved in the national cancer and death registries in
129 the Swedish cohort. Follow-up time started on the date of thyroid cancer diagnosis and ended
130 on the date of any second cancer diagnosis (except non-melanoma skin cancer), death, last
131 visit to the treatment center, or the end of the study period (31 December 2004, 31 December
132 2008, and 31 December 2014 for the Swedish, Italian, and French cohorts, respectively),
133 whichever occurred first. We censored the follow-up at age 95 years, because beyond that
134 age, cancer records are likely to be inaccurate (n=31), and at the start date of external
135 radiotherapy, if any, in the Italian cohort because of the unavailability of technical parameters
136 needed for the dose calculation (n=14).

137 ## Reconstruction of the incidental dose to the breast

138 Because ionizing radiation effects depend on the doses absorbed by the target organ, we
139 reconstructed doses incidentally delivered by the two sources of high exposure in our study,
140 I-131 administration and external radiotherapy.

141 We estimated the mean I-131 absorbed dose, D_{r_T} (Gy), incidentally delivered to the target
142 organ r_T (i.e., the breasts) , by N administrations of I-131 either for diagnostic or therapeutic

purposes, for women aged >15 years at thyroid cancer diagnosis, using the Medical Internal Radiation Dose's formula (24):

$$D_{r_T} = \sum_{n=1}^{N} \left(A_{0,n} \times \sum_{r_S=1}^{N_S} \tilde{a}(r_S, T_D) \times S(r_T \leftarrow r_S) \right)$$

where N, the number of administrations of I-131; $A_{0,n}$, the administered activity for the nth treatment (Bq); N_S, the number of source organs; T_D, the dose-integration period (s); $\tilde{a}(r_S, T_D)$, the time-integrated activity coefficient for the source organ r_S (s); $S(r_T \leftarrow r_S)$, the value representing the mean absorbed dose rate per unit activity from source organ to target organ (Gy/(Bq.s)). The S values vary according to the source-target region pair (25, 26), and were computed with the reference female voxel phantoms developed by the International Commission on Radiological Protection (27). The time-integrated activity coefficients $\tilde{a}(r_S, T_D)$ were estimated using data of patients treated for a thyroid cancer in a previous study (28) (Supplemental method 1). I-131 activities for diagnostic purposes were not systematically recorded in all cancer centers and when available, the information on whether I-131 administration was for diagnostic or therapeutic purposes was not recorded. Therefore, we considered activities of 10 mCi (equivalent to 0.37 GBq) or more as therapeutic I-131 and lower activities as I-131 for diagnosis. We used data on therapeutic I-131 to conduct our main analyses and data on therapeutic and diagnostic I-131 for a sensitivity analysis.

External radiotherapy data were obtained from technical radiotherapy records for 503 patients (51.9%) who had received external radiotherapy. For each of these patients, absorbed doses to anatomical organs in the beam and at a distance were estimated using female mathematical phantoms corresponding to the patients' age and height at the time of treatment (29, 30), and radiotherapy equipment parameters at each cancer center. The

phantoms were simulated by a home-made computer program called “Dos_EG”, and provided 188 points of the body for dose distribution estimations (31). For patients with available technical records, we calculated the mean dose to five points located at four different quadrants (upper-inner, lower-inner, upper-outer, lower-outer) and the nipple of each breast, and subsequently calculated the mean dose to the left and the right breasts. We performed nearest neighbor hot-deck imputation (32, 33) within each cancer center for 467 (48.1%) patients without the necessary data.

Statistical analysis

We computed standardized incidence ratios (SIRs - the ratio of observed to expected number of breast cancer cases) and 95% confidence intervals (CIs), assuming a Poisson distribution for the observed number. Expected numbers of cases were calculated by applying the sex-, age-, and calendar year-specific incident rates to the appropriate person-years at risk in each country. The reference rates for the French, Italian, and Swedish cohorts were from the estimations of cancer incidence in France (period 1980–2012) (34), the registry of Varese, Lombardy (data availability starting since 1978) (35), and the Swedish national cancer registry (data availability starting since 1970) (36), respectively. In the French cohort, we used the registry of Varese as the reference rates for 178 patients who came from Italy. To compute the expected number of breast cancer cases before the availability of the reference sources, we considered the rate from the nearest available period of time for each country. We also stratified SIRs according to age at thyroid cancer diagnosis (<30/ 30-40/ 40-50/ ≥50 years of age), year at thyroid cancer diagnosis (≤1960/ 1960-1980/ >1980), and follow-up time (≤10/ 10-20/ >20 years).

The use of I-131 treatment (yes/no) and cumulative activity (no I-131 treatment/ <40/ 40-100/ 100-200/ 200-400/ ≥400 mCi) were analyzed as time-dependent variables. We supposed ten years as the shortest time needed for the development and detection of breast cancer after I-131 treatment or external radiotherapy (hereafter, minimal latency time), in agreement with previous studies (37-39). Accordingly, the relative risk (RR) of subsequent breast cancer at a given calendar period and attained age was modeled as a function of the expected number of breast cancer from the reference rates, and of the cumulative activity of I-131 treatment administered ten years or more before. We further adjusted for country, age at thyroid cancer diagnosis and cumulative dose of external radiotherapy except where stated otherwise.

The absolute excess risk (AER) was calculated as the observed minus expected number of neoplasms, divided by the person-years at risk and multiplied by 10,000. We also estimated excess relative risks (ERRs) per 100 mCi (3.7 GBq), and evaluated possible departures from linearity for the shape of dose-response models for therapeutic I-131 cumulative activity by comparing models with linear terms, linear-quadratic terms, and linear-exponential terms (Supplementary method 2). Possible effect modifications by external radiotherapy, age/year at diagnosis and follow-up time were evaluated by testing the statistical significance of an interaction term between I-131 treatment and the studied covariate (likelihood-ratio χ^2 tests). Because of the differential between number of I-131 administration for adjuvant therapy and for distant metastases and the current recommended activities in a single administration of <200 mCi (40), we stratified the risk estimates according to the number of administered activity (1/ >1) and the maximum activity in a single administration (200/ ≥200 mCi).

Several sensitivity analyses were conducted. We computed risk estimates incorporating both I-131 activities for diagnostic and therapeutic purposes. As the external radiation dose was

imputed in a considerable proportion of women treated with external radiotherapy (48.1%), we censored women after 10 years of external radiotherapy. We also set 31 December 2003 and 31 December 2009 as the end point of the study for the Italian and French cohorts, respectively, since without a recurrence, medical surveillance is more likely to be less frequent after five years of diagnosis. We also evaluated the association between breast cancer risk and I-131 estimated cumulative absorbed doses among women aged >15 years at thyroid cancer diagnosis. Because I-131-treated women could be different from women without I-131 treatment in terms of indications, and lost of follow-up, we conducted several analyses to further understand to which extent this could bias the risk estimates: First, we considered lost of follow-up as our primary outcome (instead of breast cancer diagnoses) in a sensitivity analysis. Second, we applied inverse probability weighting (IPW) accounting for the probability of receiving I-131 treatment, external radiotherapy and of lost of follow-up (Supplementary method 3).

Analyses were performed using SAS software (SAS Inc., Cary, NC) and the EPICURE AMFIT statistical software package. 95% confidence intervals (CIs) were estimated with maximum likelihood methods. When lower bounds could not be estimated, results from Wald estimation were calculated.

Results

In the pooled cohort of 8475 women treated for thyroid cancer, 5,292 (62%) were treated with I-131 treatment and 970 (11.4%) with external radiotherapy (Table 1). I-131-treated patients received a median cumulative activity of 100 mCi (range 10-1,597 mCi) – equivalent to 3.7 GBq. The median cumulative doses to the breasts from I-131 therapy and external radiotherapy were 247 mGy (range 25-3,942 mGy), and 566 mGy (range 1-46,595 mGy),

respectively (Table 1). Compared to women without I-131 treatment, I-131-treated women were more likely to be lost of follow-up, and to receive diagnostic I-131, but not external radiotherapy (Supplementary tables 1-2).

During a median follow-up of 12.7 years, 335 women developed a breast cancer, i.e. 1.52 times more than expected from the general population rates (95%CI 1.36-1.69) (Table 2). This ratio did not substantially vary among the cohorts (p-Cochran's test=0.16), but decreased with age at thyroid cancer diagnosis, and increased with follow-up and calendar year at thyroid cancer diagnosis (p-trends<0.001).

We found no evidence of departure from linearity in the shape of dose-response models for I-131 activities. Overall, we found no significant association between I-131 therapy and subsequent breast cancer risk (RR=1.07, 95%CI 0.84-1.35, AER per 10,000 person-years=0.8, 95%CI: -4.9-6.4). However, there was a significant increased risk with increasing I-131 activity (ERR per 100 mCi = 17%, 95%CI: 2 to 38%), corresponding to an ERR per 100 mGy of 5% (95%CI: 0 to 14%). The highest risk was among women who received a cumulative I-131 activity of ≥400 mCi (RR=2.41, 95%CI 1.13-3.52, AER per 10,000 person-years=42, 95%CI: -8 to 93) (Table 3).

The risk estimates remained consistent among women with a maximum activity <200 mCi (7.4 GBq) in a single administration. Stratification by the number of I-131 administrations had little influence on the risk estimates, except an increased risk among women who received a single administration of 200-400 mCi (RR=2.45, 95%CI 1.10-4.67), based on a few cases. (Table 4). We found neither significant modifying effects of other factors (Supplementary table 3), nor substantial difference between the main analyses and the sensitivity analyses. Analysis accounting for IPW even showed a stronger effect of I-131 treatment (Supplementary table 4).

Discussion

In the current study, female thyroid cancer survivors had a 1.5-fold higher rate of developing breast cancer compared to the general population. Accounting for a 10-year minimal latency time, we found a linear dose–response relationship between I-131 cumulative activities and breast cancer risk with a significant ERR per 100 mCi of 17% (equivalent to an ERR per 100 mGy of 5%). We estimated that among women with a very high cumulative I-131 activity (≥400 mCi), 42 I-131-induced breast cancer cases could occur for each 10,000 person-years.

Exposure to ionizing radiation has been demonstrated to increase the lifetime risk of breast cancer among women (37). However, the ionizing radiation-related estimated risks varied considerably across medically, occupationally, environmentally exposed populations in the previous studies. However, our increased risk of 5% per 100 mGy of I-131 absorbed dose to the breasts was 2-4 fold higher than the risk associated with external radiation therapy among cancer survivors (ERR/100 mGy varied from 0.01 to 0.03) (41), but of the same magnitude than the risk estimates reported from the US Radiologic Technologists Study (ERR/100 mGy=0.07, 95%CI: -0.01-0.19) (42), the Life Span Study of Atomic Bomb Survivors (ERR/100 mGy varied from 0.09 to 0.11) (43, 44), and the Techa River Incidence Cohort (ERR/100 mGy: 0.19, 95%CI: -0.06-0.61) (45). The discrepancy could possibly due to differences in radiation sources (e.g. dose rate), dose ranges, age at exposure, and background risks. Hypotheses and approximations used for the dose reconstruction might also contribute to the differences. Whereas the absorbed dose from I-131 depends on the distance between the source organs and the target, we used reference dose coefficients, i.e., S-values, to compute breast doses without accounting for the specific anatomy of each patient, which was lacking from the available treatment records.

We found that women with a very high cumulative activity of I-131 (≥400 mCi) were at the highest risk of subsequent breast cancer. A few previous studies with available data on I-131 cumulative activity found no higher risks related to a I-131 cumulative activity of up to >4.4 GBq or 150 mCi, after adjusting for important confounders (12, 15, 16). However, previous studies showed that that minimal latency time between (external) radiation exposure and breast cancer incidence is likely to be around 10-15 years (37, 39). This is in agreement with findings in an ad hoc analysis in our study: Considering a 5-year minimal latency time, we found a lower goodness-of-fit of the dose-response model (ERR = 12%, 95%CI -1% to 29%, p-trend=0.10) than when considering a 10-year minimal latency time. Given the long latency time of radiation-induced breast cancers (37-39), breast cancer risk associated with I-131 treatment might have been underestimated in studies with short follow-up times (12, 15, 16).

In our study, the lack of evidence of an effect modification by age at thyroid cancer diagnosis could be explained by a large proportion of patients diagnosed at the age of adulthood (80% of patients aged ≥30 years at thyroid cancer diagnosis). Individuals exposed to ionizing radiation are the most radiosensitive at early ages, mostly before the age of 30 (37, 44), and the highest risks are found around menarche (44). The low-dose range of radiation and relatively small number of breast cancer cases in early age categories limited our ability to detect an effect modification in this setting. In the current study, we were not able to obtain reliable risk estimates related to the use of external radiotherapy due to the limited number of cases (46 breast cancer cases among external radiotherapy-treated women, including 11 cases among women with a dose of ≥1 Gy), which also did not allow us to further investigate the interaction between internal-external radiation.

Although the increased risk of breast cancer among women with a high cumulative activity of I-131 is biologically plausible and line with numerous epidemiological studies on (external) radiation exposure, our results could also be due – at least in part - to indication bias, selection bias due to lost of follow-up, and surveillance bias. Thyroid cancer survivors who received a high cumulative activity of I-131 could have worse prognostic factors and a higher probability of cancer recurrence (40, 46), which require further management, possibly leading to a better follow-up and a more intensive screening strategy than women without I-131 treatment or with lower cumulative activity. However, to date, no specific breast cancer screening program has been recommended for thyroid cancer survivors. Analyses considering a long latency time of 10 years after the exposure of I-131 also minimized the impact of a potential surveillance bias. Restricting analyses to the Swedish population which has a complete, passive (non-selected) follow-up for all individuals through the national registries did not substantially change the risk estimates. Surprisingly, the results from sensitivity analyses which had considered lost of follow-up as an outcome or used inverse probability weighting (that aimed to neutralize the differences caused by a possible indication and/or selection bias) suggested that the risk could have been underestimated among women with the highest cumulative activities of I-131.

The current study has major strengths, including a large population size from three major cohorts, with confirmed thyroid cancer diagnosis and a long follow-up periods, which is crucial since the possible effects of I-131 are considered to be modest and can be subject to long latency times. The pooled cohort also includes detailed information on administration dates, and activities for I-131 treatment and external radiotherapy. To investigate breast cancer risk associated with I-131 treatment, we were able to use both administered activities and the estimate of absorbed doses, which enabled us to yield risk estimates more precisely and

compare results with previous studies. In addition to an external comparison group with the general population, we also had an internal comparison group of thyroid cancer patients who did not receive I-131 treatment, which helped us to minimize indication bias.

We acknowledge several limitations. Details on cancer stage, grade, as well as breast cancer form (unilateral or bilateral), and receptor status were unavailable. Lack of information on relevant confounders such as obesity, hormonal factors requires caution when interpreting the results. Besides, some genetic characteristics/disorders such as Cowden syndrome are common causes of both thyroid and breast cancer and we were not able to account for those factors in the current study. We were not able to estimate reliable absorbed doses from I-131 administrations for women aged 15 years or less at thyroid cancer diagnosis, and the risk estimates related to I-131 absorbed dose might not be transposable to this population. Finally, we could not obtain information on diagnostic I-131 administrations or estimate doses to the external radiotherapy for the whole population.

In conclusion, we found a higher risk of breast cancer among women treated for thyroid cancer compared to the general population, which could be partly attributable to I-131 treatment. The estimated attributable risk related to exposure to a cumulative activity of I-131 of ≥400 mCi could translate into 42 breast cancer cases in excess for every 10,000 person-years. Further investigation is needed to confirm the risks related to exposure of I-131 and to investigate the interaction with potential effect modifiers.

References

1. Ferlay J EM, Lam F, Colombet M, Mery L, Piñeros M, Znaor A, Soerjomataram I, Bray F Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer. https://gco.iarc.fr/today. (Last accessed on 05 January, 2021).
2. Kitahara CM, Sosa JA 2016 The changing incidence of thyroid cancer. Nature reviews Endocrinology **12**:646-653.
3. Li M, Dal Maso L, Vaccarella S 2020 Global trends in thyroid cancer incidence and the impact of overdiagnosis. The lancet Diabetes & endocrinology **8**:468-470.
4. Gilliland FD, Hunt WC, Morris DM, Key CR 1997 Prognostic factors for thyroid carcinoma. A population-based study of 15,698 cases from the Surveillance, Epidemiology and End Results (SEER) program 1973-1991. Cancer **79**:564-573.
5. Subramanian S, Goldstein DP, Parlea L, Thabane L, Ezzat S, Ibrahim-Zada I, Straus S, Brierley JD, Tsang RW, Gafni A, Rotstein L, Sawka AM 2007 Second primary malignancy risk in thyroid cancer survivors: a systematic review and meta-analysis. Thyroid : official journal of the American Thyroid Association **17**:1277-1288.
6. Nielsen SM, White MG, Hong S, Aschebrook-Kilfoy B, Kaplan EL, Angelos P, Kulkarni SA, Olopade OI, Grogan RH 2016 The Breast-Thyroid Cancer Link: A Systematic Review and Meta-analysis. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology **25**:231-238.
7. Reiners C, Schneider R, Platonova T, Fridman M, Malzahn U, Mäder U, Vrachimis A, Bogdanova T, Krajewska J, Elisei R, Vaisman F, Mihailovic J, Costa G, Drozd V 2020 Breast Cancer After Treatment of Differentiated Thyroid Cancer With Radioiodine in Young Females: What We Know and How to Investigate Open Questions. Review of the Literature and Results of a Multi-Registry Survey. Frontiers in endocrinology **11**:381.
8. Council NR 2006 Health Risks from Exposure to Low Levels of Ionizing Radiation: BEIR VII Phase 2. The National Academies Press, Washington, DC.
9. Clement SC, Peeters RP, Ronckers CM, Links TP, van den Heuvel-Eibrink MM, Nieveen van Dijkum EJ, van Rijn RR, van der Pal HJ, Neggers SJ, Kremer LC, van Eck-Smit BL, van Santen HM 2015 Intermediate and long-term adverse effects of radioiodine therapy for differentiated thyroid carcinoma--a systematic review. Cancer treatment reviews **41**:925-934.
10. Pukkala E, Kesminiene A, Poliakov S, Ryzhov A, Drozdovitch V, Kovgan L, Kyyrönen P, Malakhova IV, Gulak L, Cardis E 2006 Breast cancer in Belarus and Ukraine after the Chernobyl accident. International journal of cancer **119**:651-658.
11. Rivkind N, Stepanenko V, Belukha I, Guenthoer J, Kopecky KJ, Kulikov S, Kurnosova I, Onstad L, Porter P, Shklovskiy-Kordi N, Troshin V, Voillequé P, Davis S 2020 Female breast cancer risk in Bryansk Oblast, Russia, following prolonged low dose rate exposure to radiation from the Chernobyl power station accident. International journal of epidemiology **49**:448-456.
12. Lin CY, Lin CL, Huang WS, Kao CH 2016 Risk of Breast Cancer in Patients with Thyroid Cancer Receiving or Not Receiving 131I Treatment: A Nationwide Population-Based Cohort Study. Journal of nuclear medicine : official publication, Society of Nuclear Medicine **57**:685-690.
13. Zhang Y, Liang J, Li H, Cong H, Lin Y 2016 Risk of second primary breast cancer after radioactive iodine treatment in thyroid cancer: a systematic review and meta-analysis. Nuclear medicine communications **37**:110-115.
14. Yu CY, Saeed O, Goldberg AS, Farooq S, Fazelzad R, Goldstein DP, Tsang RW, Brierley JD, Ezzat S, Thabane L, Goldsmith CH, Sawka AM 2018 A Systematic Review and Meta-Analysis of Subsequent Malignant Neoplasm Risk After Radioactive Iodine Treatment of Thyroid Cancer. Thyroid : official journal of the American Thyroid Association **28**:1662-1673.
15. Ahn HY, Min HS, Yeo Y, Ma SH, Hwang Y, An JH, Choi HS, Keam B, Im SA, Park DJ, Park IA, Noh DY, Youn YK, Chung JK, Cho BY, Park SK, Park YJ 2015 Radioactive Iodine Therapy Did Not

Significantly Increase the Incidence and Recurrence of Subsequent Breast Cancer. The Journal of clinical endocrinology and metabolism **100**:3486-3493.

16. Teng CJ, Hu YW, Chen SC, Yeh CM, Chiang HL, Chen TJ, Liu CJ 2016 Use of Radioactive Iodine for Thyroid Cancer and Risk of Second Primary Malignancy: A Nationwide Population-Based Study. Journal of the National Cancer Institute **108**.

17. Verkooijen RB, Smit JW, Romijn JA, Stokkel MP 2006 The incidence of second primary tumors in thyroid cancer patients is increased, but not related to treatment of thyroid cancer. European journal of endocrinology **155**:801-806.

18. Brown AP, Chen J, Hitchcock YJ, Szabo A, Shrieve DC, Tward JD 2008 The risk of second primary malignancies up to three decades after the treatment of differentiated thyroid cancer. The Journal of clinical endocrinology and metabolism **93**:504-515.

19. Iyer NG, Morris LG, Tuttle RM, Shaha AR, Ganly I 2011 Rising incidence of second cancers in patients with low-risk (T1N0) thyroid cancer who receive radioactive iodine therapy. Cancer **117**:4439-4446.

20. Rubino C, de Vathaire F, Dottorini ME, Hall P, Schvartz C, Couette JE, Dondon MG, Abbas MT, Langlois C, Schlumberger M 2003 Second primary malignancies in thyroid cancer patients. British journal of cancer **89**:1638-1644.

21. Hall P, Holm LE, Lundell G, Bjelkengren G, Larsson LG, Lindberg S, Tennvall J, Wicklund H, Boice JD, Jr. 1991 Cancer risks in thyroid cancer patients. British journal of cancer **64**:159-163.

22. Dottorini ME, Lomuscio G, Mazzucchelli L, Vignati A, Colombo L 1995 Assessment of female fertility and carcinogenesis after iodine-131 therapy for differentiated thyroid carcinoma. Journal of nuclear medicine : official publication, Society of Nuclear Medicine **36**:21-27.

23. de Vathaire F, Schlumberger M, Delisle MJ, Francese C, Challeton C, de la Genardiére E, Meunier F, Parmentier C, Hill C, Sancho-Garnier H 1997 Leukaemias and cancers following iodine-131 administration for thyroid cancer. British journal of cancer **75**:734-739.

24. Bolch WE, Eckerman KF, Sgouros G, Thomas SR 2009 MIRD pamphlet No. 21: a generalized schema for radiopharmaceutical dosimetry--standardization of nomenclature. Journal of nuclear medicine : official publication, Society of Nuclear Medicine **50**:477-484.

25. Lamart S, Simon SL, Bouville A, Moroz BE, Lee C 2016 S values for 131I based on the ICRP adult voxel phantoms. Radiat Prot Dosimetry **168**:92-110.

26. Lamart S, Bouville A, Simon SL, Eckerman KF, Melo D, Lee C 2011 Comparison of internal dosimetry factors for three classes of adult computational phantoms with emphasis on I-131 in the thyroid. Physics in medicine and biology **56**:7317-7335.

27. ICRP. 2009 Adult reference computational phantoms. Annals of the ICRP **39**:1-166.

28. Remy H, Borget I, Leboulleux S, Guilabert N, Lavielle F, Garsi J, Bournaud C, Gupta S, Schlumberger M, Ricard M 2008 131I effective half-life and dosimetry in thyroid cancer patients. Journal of nuclear medicine : official publication, Society of Nuclear Medicine **49**:1445-1450.

29. Francois P, Beurtheret C, Dutreix A 1988 Calculation of the dose delivered to organs outside the radiation beams. Medical physics **15**:879-883.

30. Francois P, Beurtheret C, Dutreix A, De Vathaire F 1988 A mathematical child phantom for the calculation of dose to the organs at risk. Medical physics **15**:328-333.

31. Diallo I, Lamon A, Shamsaldin A, Grimaud E, de Vathaire F, Chavaudra J 1996 Estimation of the radiation dose delivered to any point outside the target volume per patient treated with external beam radiotherapy. Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology **38**:269-271.

32. Little RJ, Rubin DB 2019 Statistical analysis with missing data. Vol 793. John Wiley & Sons.

33. Andridge RR, Little RJ 2010 A Review of Hot Deck Imputation for Survey Non-response. International statistical review = Revue internationale de statistique **78**:40-64.

34. Binder-Foucard F, Bossard N, Delafosse P, Belot A, Woronoff AS, Remontet L 2014 Cancer incidence and mortality in France over the 1980–2012 period: Solid tumors. Revue d'Épidémiologie et de Santé Publique **62**:95-108.

35. Bray F, Ferlay J, Laversanne M, Brewster DH, Gombe Mbalawa C, Kohler B, Piñeros M, Steliarova-Foucher E, Swaminathan R, Antoni S, Soerjomataram I, Forman D 2015 Cancer Incidence in Five Continents: Inclusion criteria, highlights from Volume X and the global status of cancer registration. International journal of cancer **137**:2060-2071.

36. National Board of Health and Welfare. Cancer incidence in Sweden. https://sdb.socialstyrelsen.se/if_can/val_eng.aspx. (Last accessed on 21 October, 2020).

37. Preston DL, Mattsson A, Holmberg E, Shore R, Hildreth NG, Boice JD, Jr. 2002 Radiation effects on breast cancer risk: a pooled analysis of eight cohorts. Radiat Res **158**:220-235.

38. Ronckers CM, Erdmann CA, Land CE 2005 Radiation and breast cancer: a review of current evidence. Breast cancer research : BCR **7**:21-32.

39. Land CE, Tokunaga M, Koyama K, Soda M, Preston DL, Nishimori I, Tokuoka S 2003 Incidence of female breast cancer among atomic bomb survivors, Hiroshima and Nagasaki, 1950-1990. Radiation research **160**:707-717.

40. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, Pacini F, Randolph GW, Sawka AM, Schlumberger M, Schuff KG, Sherman SI, Sosa JA, Steward DL, Tuttle RM, Wartofsky L 2016 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid : official journal of the American Thyroid Association **26**:1-133.

41. Berrington de Gonzalez A, Gilbert E, Curtis R, Inskip P, Kleinerman R, Morton L, Rajaraman P, Little MP 2013 Second solid cancers after radiation therapy: a systematic review of the epidemiologic studies of the radiation dose-response relationship. Int J Radiat Oncol Biol Phys **86**:224-233.

42. Preston DL, Kitahara CM, Freedman DM, Sigurdson AJ, Simon SL, Little MP, Cahoon EK, Rajaraman P, Miller JS, Alexander BH, Doody MM, Linet MS 2016 Breast cancer risk and protracted low-to-moderate dose occupational radiation exposure in the US Radiologic Technologists Cohort, 1983-2008. British journal of cancer **115**:1105-1112.

43. Preston DL, Ron E, Tokuoka S, Funamoto S, Nishi N, Soda M, Mabuchi K, Kodama K 2007 Solid cancer incidence in atomic bomb survivors: 1958-1998. Radiation research **168**:1-64.

44. Brenner AV, Preston DL, Sakata R, Sugiyama H, de Gonzalez AB, French B, Utada M, Cahoon EK, Sadakane A, Ozasa K, Grant EJ, Mabuchi K 2018 Incidence of Breast Cancer in the Life Span Study of Atomic Bomb Survivors: 1958-2009. Radiation research **190**:433-444.

45. Davis FG, Yu KL, Preston D, Epifanova S, Degteva M, Akleyev AV 2015 Solid Cancer Incidence in the Techa River Incidence Cohort: 1956-2007. Radiation research **184**:56-65.

46. Luster M, Clarke SE, Dietlein M, Lassmann M, Lind P, Oyen WJ, Tennvall J, Bombardieri E 2008 Guidelines for radioiodine therapy of differentiated thyroid cancer. European journal of nuclear medicine and molecular imaging **35**:1941-1959.

Additional information

Acknowledgement

xxxxx

Ethics approval and consent to participate

This study was performed under xxxx.

Authors' contributions

Study conception, and design: F.D.V., C.R, T.T.V.T, xxxxx. Statistical analysis: T.T.V.T. Writing of the original draft: T.T.V.T. Interpretation of the results: F.D.V., T.T.V.T, C.R, N.J., xxxx. All authors revised the paper and approved the final version.

Author disclosure statement

The authors declare no conflict of interest

Funding information

Thi-Van-Trinh TRAN received a doctoral grant from the Paris Sud-Paris Saclay University. This work was funded by the Epidemiology Commission of Electricity of France (EDF) and the EPIRADBIO European project (grant n°###).

Figure 1: Flowchart of the study

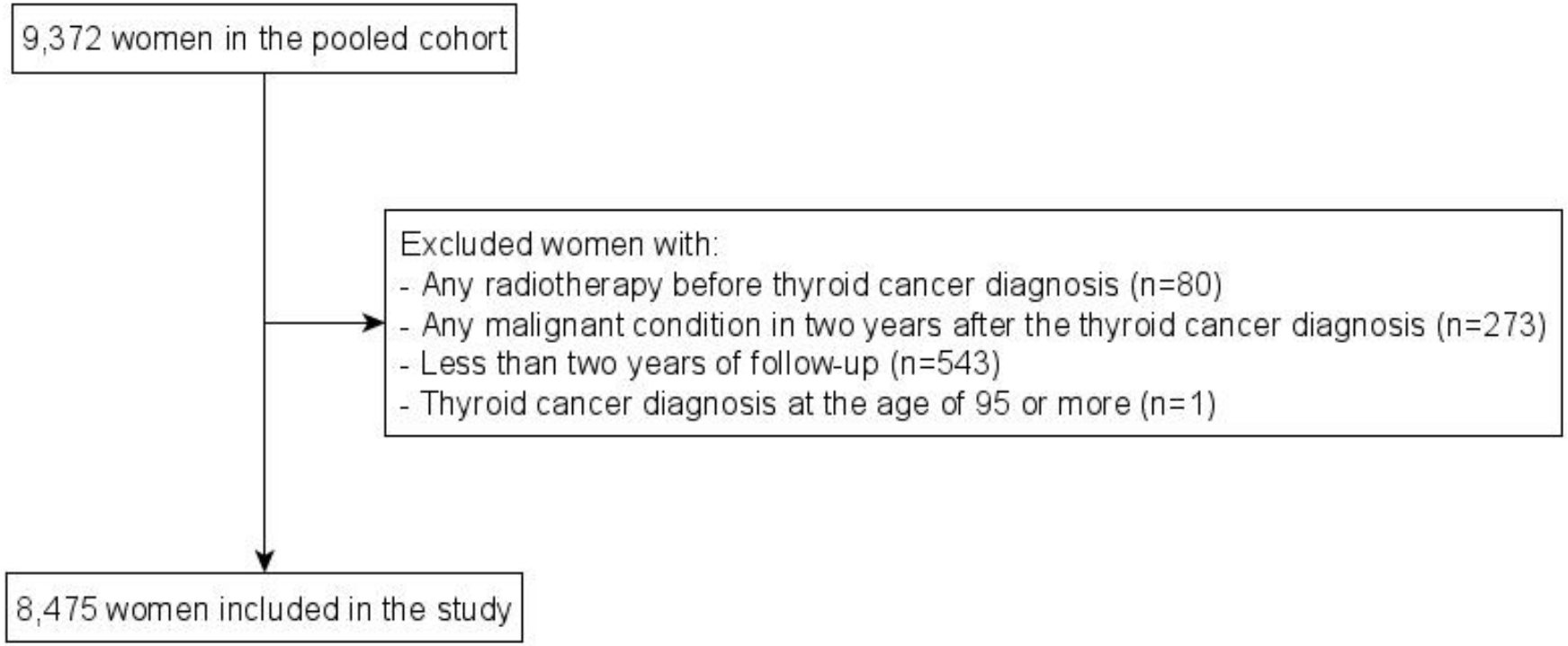


Table 1: Characteristics of the pooled cohort

	France	Italia[1]	Sweden	Pooled cohort
	(N=5,469)	(N=1,551)	(N=1,455)	(N=8,475)
Year of treatment, year, median (min-max)	1993 (1934-2005)	1988 (1958-1996)	1965 (1950-1983)	1989 (1934-2005)
Age at thyroid cancer diagnosis, year, mean (min-max)	44 (2-90)	44 (5-81)	49 (5-90)	44.5 (2-90)
Follow-up time, year, median (min-max)	12 (2-66.5)	11 (2-37)	24 (2-55)	12.7 (2.0-66.5)
Breast cancer cases, n (%)	202 (3.7)	38 (2.5)	95 (6.5)	335 (4.0)
Time to breast cancer, year, median (min-max)	12 (2-55)	12 (2-35)	25 (2-46)	14.1 (2.0-55.2)
Treatment of thyroid cancer by ionising radiation				
External radiotherapy, n (%)	430 (8)	-	540 (37)	970 (11.4)
Therapeutic I-131 activity, n (%)	3,403 (62)	1307 (84)	582 (40)	5,292 (62)
- Number of therapeutic I-131 activity, median (min-max)	1 (1-14)	1 (1-15)	1 (1-10)	1 (1-15)
- Cumulative activity of therapeutic I-131, mCi, median (min-max)	100 (10-1,597)	100 (25-1,491)	75 (10-1,330)	100 (10-1,597)
Cumulative radiation dose delivered to the breasts				
Therapeutic I-131 activity, mGy, median (min-max)[2]	247 (25-3,942)	247 (61-3,680)	185 (25-3,283)	247 (25-3,942)
External radiotherapy , mGy, median (min-max)	1299 (10-43,480)	-	272 (1-46,595)	566 (1-46,595)
- Imputed dosimetry for external radiotherapy, n (%)	61 (14)	0	406 (75)	467 (48)

[1] Patients with external radiotherapy were excluded at inclusion or censored at the start date of external radiotherapy

[2] Patients aged >15 years at thyroid cancer diagnosis

Table 2: Observed number of breast cancer cases, standardized incidence ratio (95% confidence interval) in the pooled cohort

	France		Sweden		Italia		Pooled cohort	
	BC cases/PY	**SIR (95%CI)**	**BC cases/PY**	**SIR (95%CI)**	**BC cases/PY**	**SIR (95%CI)**	**BC cases/PY**	**SIR (95%CI)**
Overall	198/65,249	1.67 (1.44-1.91)	95/30,960	1.35 (1.10-1.64)	42/17,191	1.33 (0.97-1.78)	335/11,3400	1.52 (1.36-1.69)
Age at thyroid cancer diagnosis (year)								
<30	26/15,692	2.29 (1.52-3.28)	28/7,144	3.74 (2.52-5.30)	7/4,118	3.01 (1.29-5.82)	61/26,954	2.87 (2.21-3.66)
30-40	54/15,444	2.22 (1.68-2.87)	26/6,803	2.17 (1.44-3.11)	8/4,120	1.27 (0.58-2.36)	88/26,367	2.06 (1.66-2.53)
40-50	52/15,954	1.44 (1.08-1.87)	21/7,445	1.16 (0.73-1.72)	14/4,409	1.38 (0.78-2.23)	87/27,807	1.35 (1.09-1.65)
≥50	66/18,160	1.40 (1.09-1.77)	20/9,568	0.61 (0.38-0.92)	13/4,544	1.02 (0.56-1.68)	99/32,272	1.07 (0.87-1.29)
P-heterogeneity		*<0.001*		*<0.001*		*0.099*		*<0.001*
P-trend		*<0.001*		*0.325*		*0.433*		*0.002*
Year of thyroid cancer diagnosis								
≤1960	8/3,077	1.47 (0.67-2.74)	26/9,187	1.21 (0.81-1.75)	0/154	-	34/12,418	1.26 (0.89-1.73)
1960-1980	45/16,435	1.57 (1.15-2.07)	69/21,752	1.41 (1.10-1.77)	12/3,370	2.09 (1.12-3.51)	126/41,558	1.51 (1.26-1.79)
>1980	145/45,737	1.71 (1.45-2.00)	0/21	-	30/13,667	1.18 (0.80-1.65)	175/59,425	1.59 (1.36-1.83)
P-heterogeneity		*<0.001*		*0.042*		*0.090*		*<0.001*
P-trend		*<0.001*		-		-		*<0.001*
Follow-up time (years)								
≤10	78/35,251	1.37 (1.09-1.70)	15/9,879	0.74 (0.43-1.19)	19/10,921	1.08 (0.67-1.65)	112/56,051	1.19 (0.99-1.42)
10-20	68/20,740	1.67 (1.31-2.10)	23/9,496	1.11 (0.71-1.62)	13/5,251	1.15 (0.63-1.90)	104/35,487	1.43 (1.17-1.72)
>20	52/9,258	2.43 (1.83-3.15)	57/11,586	1.93 (1.47-2.48)	10/1,019	3.73 (1.87-6.54)	119/21,863	2.22 (1.85-2.64)
P-heterogeneity		*<0.001*		*<0.001*		*0.007*		*<0.001*
P-trend		*<0.001*		*<0.001*		*0.008*		*<0.001*

BC: Breast cancer, CI: Confidence interval, PY: Person-year, SIR: Standardized incidence ratio

Table 3: Breast cancer risk associated with therapeutic I-131 (considering a ten-year minimal latency time)

	Pooled cohort		
	BC cases/Person-years	**RR[1] (95%CI)**	**AER[2]**
Therapeutic I-131 activity			
No	234/85,715	1	
Yes	101/27,685	1.07 (0.84-1.35)	
P-heterogeneity		*>0.5*	
Cumulative activity of therapeutic I-131 (mCi)			
No I-131 treatment	234/85,715	1	
<40	4/2,316	0.49 (0.15-1.15)	
40-100	16/6,499	0.77 (0.44-1.25)	
100-200	53/14,029	1.10 (0.80-1.47)	
200-400	19/3,731	1.55 (0.92-2.44)	
≥400	9/1112	2.41 (1.13-4.52)	42 (-8-93)[3]
P-heterogeneity		*0.039*	
P-trend		*0.028*	
ERR per 100 mCi[1]		0.17 (0.02-0.38)	
ERR per 100 mCi among women who received I-131 treatment[1]		0.30 (0.08-0.64)	
Cumulative activity of therapeutic I-131 (mGy)[4]			
No I-131 treatment	232/83,162	1	
<100	5/2,644	0.54 (0.19-1.18)	
100-250	52/16,637	0.91 (0.67-1.22)	
250-500	20/4,682	1.26 (0.76-1.95)	
500-1000	16/2,043	2.34 (1.33-3.81)	37 (4-82)
≥1000	3/697	1.20 (0.29-3.18)	
P-heterogeneity		*0.033*	
P-trend		*0.094*	
ERR per 100 mGy[1,4]		0.05 (0.00-0.14)	
ERR per 100 mGy among women who received I-131 treatment[1,4]		0.10 (0.01-0.24)	

AER: Absolute excess risk per 10,000 person-years, BC: Breast cancer, CI: Confidence interval, ERR: Excess relative risk, RR: Relative risk

[1] Adjusted for country, age at diagnosis, and dose of external radiotherapy delivered to the breast in the background risks

[2] AER are shown only when the corresponding RRs were statistically significant at $P < 0.05$

[3] Wald estimation

[4] Analysis conducted among women aged >15 years at thyroid cancer diagnosis

Table 4: Breast cancer risk associated with therapeutic I-131 stratified by the number of administered activity and the maximum activity in a single administration to the breast

I-131 cumulative activity (mCi)	10-year latency	
	BC cases	RR (95%CI)
No I-131 treatment	234	1
Number of administered activity		
1		
<40	4	0.51 (0.16-1.20)
40-100	16	0.80 (0.46-1.30)
100-200	49	1.09 (0.79-1.48)
200-400	8	2.45 (1.10-4.67)
≥400	0	-
>1		
<40	0	-
40-100	0	-
100-200	4	1.10 (0.34-2.62)
200-400	11	1.22 (0.62-2.15)
≥400	9	2.57 (1.20-4.84)
The maximum activity in a single administration (mCi)		
Maximum activity <200 mCi		
<40	4	0.49 (0.15-1.15)
40-100	16	0.77 (0.44-1.25)
100-200	53	1.10 (0.80-1.47)
200-400	8	1.10 (0.49-2.11)
≥400	2	3.23 (0.53-10.37)
Maximum activity ≥200 mCi		
200-400	11	2.18 (1.11-3.83)
≥400	7	2.24 (0.94-4.48)

BC: Breast cancer, CI: Confidence interval, RR: Relative risk

université PARIS-SACLAY | ÉCOLE DOCTORALE Santé Publique (EDSP)

Title: Association between thyroid dysfunction and breast cancer risk among adult women

Keywords: Thyroid dysfunction, hyperthyroidism, hypothyroidism, radioactive iodine, breast cancer, cohorts

Abstract: Long-term outcomes of thyroid dysfunction (hyper- and hypothyroidism) among adult women remain unclear, with continuing debates on the effect of abnormal thyroid hormone levels and thyroid dysfunction treatments (e.g radioactive iodine - RAI) on cancer risk. This thesis project aimed to evaluate the association between the risk of female breast cancer and thyroid dysfunction, while accounting for thyroid dysfunction treatments, comorbidities, and breast cancer risk factors.

The project was mainly based on the UK Biobank (UKB) cohort, which included 273,375 women aged 40-69 years at inclusion between 2006 and 2010. Detailed data on personal and family medical history, medications, lifestyle, reproductive and socioeconomic characteristics were collected. The UKB cohort has been linked to regional and national hospital inpatient databases, cancer and death registries (5,326 incident breast cancer cases reported during a median follow-up time of 7 years). We found no significant association between breast cancer risk and either overall hyper- or hypothyroidism. However, breast cancer risk was ~40% higher among women treated for hyperthyroidism compared to women with no thyroid dysfunction, regardless of the treatment modality. No increased risk was observed among untreated women, suggesting an effect hyperthyroidism severity and/or etiology.

When combining those results with all evidence currently available in the litterarure, we estimated a pooled risk ratio of 1.15 and 0.86 for hyper- and hypothyroidism (treated or not), respectively, compared to no thyroid dysfunction. In the meta-analysis, breast cancer risk was significantly lower among premenopausal women with hypothyroidism, and increased, although insignificantly, among postmenopaused women with hyperthyroidism.

The analyses were extended to a European pooled cohort of 8,475 female thyroid cancer survivors (335 breast cancer cases reported during a median follow-up time of 12.7 years), to investigate the role of RAI in breast cancer incidence. We found a significant dose-response relationship between the cumulative activity of therapeutic RAI and breast cancer risk after a minimal latency time of 10 years, with no evidence of departure from linearity. The estimated excess relative risk was 0.5% per 10 mCi. This result was driven by high cumulative activity RAI (200- >400 mCi); no significant increased risk was found for lower exposures. When applied to typical RAI exposure received for hyperthyroidism treatment, the estimated relative risk translates into 0.4 excess breast cancer cases after 10000 person-years since exposure.

In conclusion, this thesis showed modest associations between thyroid dysfunction and breast cancer risk, which could not be explained by RAI exposure. Rather, the intertwined roles of hyperthyroidism etiology and blood levels of thyroid hormones and estrogens on breast cancer risk should be better characterized.

Titre : Association entre la dysfonction thyroïdienne et le risque de cancer du sein chez la femme adulte

Mots clés : Dysfonction thyroïdienne, hyperthyroïdie, hypothyroïdie, cancer du sein, iode radioactive, cohorte

Résumé : Les conséquences à long-terme de la dysfonction thyroïdienne (hyperthyroïdie, hypothyroïdie) restent insuffisamment décrites, avec un vif débat sur l'effet de niveaux anormaux d'hormones thyroïdiennes et des traitements pour la dysfonction thyroïdienne (par exemple l'iode radioactive) sur le risque de cancer. L'objectif de ce projet de thèse était d'évaluer l'association entre le risque de cancer du sein et la dysfonction thyroïdienne chez les femmes, en prenant en compte les traitements pour la dysfonction thyroïdienne, les comorbidités et les risques de facteurs du cancer du sein.

Le projet a été conduit principalement à partir de la cohorte UK Biobank, qui se compose de 273.375 femmes âgées de 40 à 69 ans à l'inclusion entre 2006 et 2010. Des données détaillées sur les antécédents médicaux personnels et familiaux, les traitements reçus, le mode de vie, les facteurs reproductifs et les caractéristiques sociodémographiques ont été recueillis à l'inclusion. La cohorte bénéficie également de données individuelles issues des registres hospitaliers régionaux et des registres nationaux de cancer et de mortalité. Les analyses portent sur 5,326 cas incidents de cancer du sein reportés au cours d'un temps de suivi médian de 7 ans. Dans la cohorte UKB, après avoir pris en compte des facteurs de risque connus, nous n'avons pas trouvé une association significative entre le risque de cancer du sein et l'hyper- et l'hypothyroïdie. Cependant, le risque de cancer du sein était ~40% plus élevé chez les femmes traitées pour l'hyperthyroïdie, par rapport aux femmes sans la dysfonction thyroïdienne, quelle que soit la modalité de traitement. Aucune augmentation du risque n'a été observée chez les femmes non traitées, ce qui suggère un effet de la sévérité et/ou de l'étiologie de l'hyperthyroïdie.

Lorsque ces résultats sont combinés avec les études précédentes disponibles dans la littérature, nous avons montré un risque poolé significatif de 1.15 et 0.86 pour l'hyper- et l'hypothyroïdie (traitée ou non), respectivement, par rapport à l'absence de dysfonctionnement thyroïdien. Dans la méta-analyse, le risque de cancer du sein a significativement diminué chez les femmes préménopausales avec l'hypothyroïdie, mais augmenté, bien que de manière non significative, chez les femmes ménopausées avec l'hyperthyroïdie.

Les analyses ont été étendues à une cohorte européenne regroupant 8 475 femmes ayant survécu à un cancer de la thyroïde (335 cas de cancer du sein ont été enregistrés au cours d'une période de suivi médiane de 12,7 ans), pour étudier le rôle de l'iode radioactive sur l'incidence de cancer du sein. Nous avons montré une association dose-effet linéaire entre l'activité cumulée du RAI et le risque de cancer du sein après un temps de latence minimum de 10 ans, sans preuve d'un écart par rapport à la linéarité. L'excès de risque de a été estimé à 0.5% par 10 mCi. Ce résultat est dû à une activité cumulative élevée (200->400 mCi); aucune augmentation significative du risque n'a été trouvée pour des expositions plus faibles. Lorsqu'il est appliqué à l'exposition typique au RAI reçue pour le traitement de l'hyperthyroïdie, le risque relatif estimé se traduit par un excès de cas de cancer du sein de 0.4 par 10 000 personne-années depuis l'exposition.

En conclusion, les résultats de ce projet mettent en évidence une association modeste entre la dysfonction thyroïdienne et le risque de cancer du sein, qui ne pourrait être qu'en partie expliquée par l'exposition au RAI. Il conviendrait plutôt de mieux caractériser les rôles entrelacés de l'étiologie de l'hyperthyroïdie et des taux sanguins d'hormones thyroïdiennes et d'œstrogènes sur le risque de cancer du sein.