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Nirmala Prajapati

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Exposure to outdoor artificial light at night, working at night and the risk of breast cancer; Findings from three studies: CECILE, E3N-Generations and CONSTANCES

*Exposition à la lumière artificielle extérieure la nuit, travail de nuit et risque de
cancer du sein ; résultats de trois études : CECILE, E3N-Génération et
CONSTANCES*

Thèse de doctorat de l'université Paris-Saclay

École doctorale n°570, Santé Publique (EDSP)

Spécialité de doctorat : Épidémiologie

Graduate School : Santé publique. Référent : Faculté de médecine

Thèse préparée dans les unités de recherche : **CESP (Université Paris-Saclay, UVSQ, Inserm)**, sous la direction de **Pascal GUÉNEL**, Directeur de recherche, Inserm, la co-direction de **Elodie FAURE**, Chef de projet, Géomaticien, Inserm.

Thèse soutenue à Paris-Saclay, le 7 novembre 2024, par

Nirmala PRAJAPATI

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RESEARCH TEAM AND FUNDING SOURCES

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RESUME

Contexte : L'incidence du cancer du sein est en constante augmentation. La modernisation rapide des sociétés et le marché du travail ont entraîné une exposition accrue à la lumière artificielle nocturne (LAN) et au travail de nuit. Ces facteurs contribuent à la perturbation du rythme circadien, un facteur de risque potentiel pour les cancers hormono-dépendants comme le cancer du sein. La littérature sur le travail de nuit, la LAN extérieure et le risque de cancer du sein reste incohérente en raison des différences entre les méthodes d'évaluation de l'exposition et la prise en compte des facteurs de confusion.

Objectifs : Cette thèse vise à étudier le rôle de l'exposition environnementale à la LAN et celui du travail de nuit sur le risque de cancer du sein en tenant compte des facteurs de confusion potentiels, à partir d'études en France.

Méthodes : L'association entre la LAN extérieure et le risque de cancer du sein a été étudiée dans l'étude cas-témoins en population, CECILE (1185 cas et 1218 témoins), et dans l'étude cas-témoins nichée dans la cohorte prospective E3N-Génération (5222 cas et 5222 témoins). L'exposition à la LAN extérieure a été évaluée à l'aide d'images satellite du programme américain de satellites météorologiques (Defense Meteorological Satellite Program). L'association entre le travail de nuit et le cancer du sein a été étudiée dans l'étude C3-Nuit, une étude cas-témoins nichée dans la cohorte CONSTANCES (671 cas et 1016 témoins). Une évaluation détaillée de l'exposition au travail de nuit a été réalisée à partir de l'historique professionnel. Des modèles de régression logistique ont été utilisés pour obtenir les estimations de risque, en tenant compte des principaux facteurs de confusion comme la pollution de l'air ou la proximité d'espaces verts (indice de végétation normalisé : Normalized Difference Vegetation Index).

Résultats : Dans l'étude CECILE et dans la cohorte E3N-génération, nous avons observé des odds ratios légèrement élevés de cancer du sein associés à l'exposition à la LAN extérieure qui persistaient après ajustement sur les co-expositions environnementales. Ces deux études suggèrent que le risque de cancer du sein lié à la LAN serait plus élevé chez les femmes ménopausées que chez celles en pré-ménopause. Une association plus marquée pour le sous-type de cancer du sein HER2+ a été observée dans l'étude CECILE.

Dans l'étude C3-Nuit, aucune association entre le travail de nuit et le risque de cancer du sein n'a été observée globalement, mais les estimations de risque étaient plus élevées chez les femmes travaillant en horaires de nuit alternants. Les associations étaient plus prononcées chez les femmes ménopausées que chez les femmes pré-ménopausées, chez celles qui avaient un chronotype du matin par rapport à celles ayant un chronotype du soir ou neutre, et chez celles qui avaient commencé à travailler de nuit avant leur première grossesse.

Conclusion : Les résultats de cette thèse suggèrent que l'exposition à la LAN extérieure et au travail de nuit, particulièrement en travail alternant, pourraient contribuer au risque de

cancer du sein, soutenant l'hypothèse d'un effet des perturbations du rythme circadien sur le risque de cancer du sein. Cependant, les limites méthodologiques, les erreurs de classement sur l'exposition, d'éventuels effets de confusion résiduels ont pu affecter la validité des associations observées. Ces résultats nécessitent confirmation par de futures études utilisant des méthodes avancées d'évaluation de l'exposition.

Mots-clés : cancer du sein, épidémiologie, étude cas-témoin, lumière artificielle nocturne, perturbation circadienne, travail de nuit

ABSTRACT

Background: The incidence of breast cancer is increasing and is projected to continue rising. Rapid modernization and growth in the global workforce have increased exposure to artificial light at night (LAN) and night shift work. These factors contribute to circadian disruption, a potential risk factor for hormone-dependent cancers, including breast cancer. Directly assessing circadian disruption through biomarkers like melatonin in large-scale epidemiological studies is resource-intensive and time-consuming. Existing literature on night shift work, outdoor LAN, and breast cancer risk remains inconsistent due to variations in exposure assessment methods and inadequate adjustment for confounders.

Objectives: This thesis aims to investigate the role of environmental exposure to outdoor LAN and night shift work in breast cancer risk in the French population.

Methods: Three epidemiological studies were utilized to achieve the objectives. The association of outdoor LAN and breast cancer risk was studied using a population-based case-control study, CECILE (1185 cases and 1218 controls), and a nested case-control study within the prospective E3N-Generation cohort (5222 cases and 5222 controls). Outdoor LAN exposure was assessed using satellite images from the Defense Meteorological Satellite Program. The association between night shift work and breast cancer risk was studied using C3-Nuit, a nested case-control study within the CONSTANCES cohort (671 cases and 1016 controls). A detailed assessment of exposure to night shift work was conducted using a comprehensive questionnaire on occupational history. Logistic regression models were used to obtain risk estimates adjusting for important confounders, including environmental exposure such as air pollution and residential greenness (Normalized Difference Vegetation Index).

Results: In the CECILE study and the E3N-Generation cohort, we found slightly increased odds ratios (ORs) of breast cancer associated with exposure to outdoor LAN that persisted after adjustment for environmental co-exposures. Both studies suggested a potential increased risk for post-menopausal women, while a stronger association for the HER2+ cancer subtype was found in the CECILE Study.

In the C3-nuit study, no clear association between night shift work and breast cancer risk was seen overall, but the ORs for breast cancer were increased among women working alternating night shifts. The associations were more pronounced among post-menopausal women than premenopausal women, those with morning chronotypes compared to evening or neutral chronotypes, and those who started night work before their first pregnancy.

Conclusions: The findings from this thesis suggest that both exposure to outdoor LAN and night shift work, particularly alternating night shift work, potentially contribute to breast cancer risk, supporting the hypothesis of the role of circadian disruption in breast cancer. However, methodological limitations, exposure misclassification, potential selection bias, and residual

confounding may undermine the validity of the observed associations. These findings warrant confirmation through future studies with refined methodologies.

Keywords: artificial light at night, breast cancer, circadian disruption, case-control study, epidemiology, night shift work

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- [Prajapati, N.](#), Cordina, E., Boileau, A., Faure, E., & Guénel, P. (2023). Artificial light at night and breast cancer risk: The findings from CECILE study (France). *European Journal of Public Health*, 33(Supplement_2), ckad160-571.

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- Exposure to outdoor artificial light at night and breast cancer risk: a population-based case-control study in two French departments (the CECILE study), Rencontre Scientifique, EHESP, Paris, March 2023

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LIST OF ABBREVIATIONS

95% CI	95% Confidence Interval
nm	Nanometer
nW/cm ² /sr	Nanowatt per Centi-Meter Squared Per Steradian
µg/m ³	Microgram per Cubic Meter
AUDIT	Alcohol Use Disorders Identification Test
BC	Breast Cancer
BCS	Breast-Conserving Surgery
BMI	Body Mass Index
BRCA1	Breast Cancer Gene 1
BRCA2	Breast Cancer Gene 2
C3-Nuit	Cancers dans la Cohorte Constances et Travail De Nuit
CA125	Cancer Antigen 125
CAPi	Computer Assisted-Personal Interview
CECILE	Cancers du Sein : Etude Epidémiologique en Côte d'Or Et En Ille-et-Vilaine Sur l'Environnement
CES	Centre d'Examen de Santé
CHIMERE	Chemistry Transport Model
CIRC	Centre International de Recherche sur le Cancer
CNAMTS	Caisse Nationale d'assurance Maladie des Travailleurs Salaries
CNAV	Caisse Nationale d'assurance Vieillesse
CONSTANCES	Cohorte des Consultants des Centres d'examens de Santé
DAG	Directed Acyclic Graph
DMSP	Defense Meteorological Satellite Program
DNA	Deoxyribonucleic Acid
DNB	Day-Night Band
E3N	Etude Epidémiologique Après De Femmes de l'Education Nationale
EPIC	European Prospective Investigation on Cancer
ER	Estrogen Receptor
FFTP	First Full Erm Pregnancy
G20	Group of Twenty
HER2	Human Epidermal Growth Factor 2
HR	Hormone Receptor

HRT	Hormone Replacement Therapy
IARC	International Agency for Research on Cancer
ICD	International Classification Of Diseases
Insee	Institut National de La Statistique et des Etudes Economiques
IQR	Interquartile Range
ISS	International Space Station
LAN	Light at Night
LED	Light Emitting Diode
LUR	Land Use Regression
MCC	Multi Case-Control
MET	Metabolic Equivalent
MGEN	Mutuelle Générale de l'Education Nationale
MRI	Magnetic Resonance Imaging
MSI	Melatonin Supression Index
NAF	Nomenclature d'activités Françaises
NDVI	Normalized Difference Vegetation Index
NO ₂	Nitrogen Dioxide
NOAA	National Oceanic and Atmospheric US Administration
OC	Oral Contraceptives
OLS	Operational Linescan System
OR	Odds Ratio
PCS	Professions et Catégories Socio-professionnelles
PM	Particulate Matter
PR	Progesterone Receptor
RGB	Red Green Blue
RR	Relative Risk
Q	Quartile
SD	Standard Deviation
SES	Socioeconomic Status
SCN	Suprachiasmatic Nuclei
SIR	Standardized Incidence Ratio
SMR	Standardized Mortality Ratio
SNDS	Système National des Données de Santé
T	Tertiles

TNBC	Triple Negative Breast Cancer
TNM	Tumour-Node-Metastasis
UK	United Kingdom
US	United States
VIF	Variance Inflation Factor
VIIRS/DNB	Visible Infrared Imaging Radiometer Suite
WHO	World Health Organization

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CHAPTER 1: GENERAL INTRODUCTION

1. ANATOMY AND PHYSIOLOGY OF BREAST

Human breasts are paired mammary glands located in the pectoral region of the anterior thorax, prominent in females after puberty but only rudimentary in males ¹. The female breast comprises 15-20 lobes surrounded by fibrous and adipose tissues. The lobes comprise many lobules with alveoli that drain into numerous lactiferous ductules, merging into one lactiferous duct and finally opening into the nipple (Fig 1). The radial arrangement of the lobules and the surrounding fibro-adipose tissues provides a tear-drop-like structure to the breast. The breast is attached to the anterior chest by the pectoralis major and minor muscles and the suspensory ligament of Cooper, while the fibrous bands within the breast tissues help maintain the position of the breast. The blood is supplied to the breasts primarily by an anastomotic network derived from the axillary, internal thoracic, and intercostal arteries. The lymphatic vessels in the breast drain the lymph to the axillary, supraclavicular, and internal mammary lymph nodes ¹.

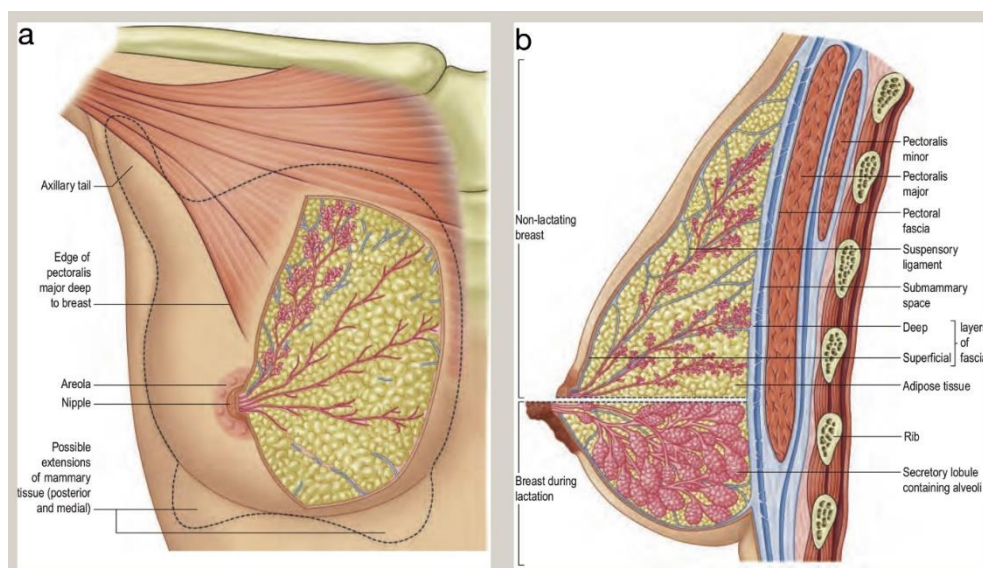


Figure 1: The structure of the breast (a) and the difference in non-lactating and lactating breast structure (b) ¹.

The anatomy and physiology of the breast change over time and are influenced and regulated by the hormonal changes during puberty, menstruation, pregnancy, lactation, and menopause ². In puberty, estrogen and growth hormones initiate duct elongation, lobule formation, and tissue growth. The changes in estrogen and progesterone during different menstrual phases cause temporary changes in breast size ³. During pregnancy and lactation, the increased estrogen, progesterone, and prolactin hormone levels induce the proliferation of the lobules

and facilitate milk production ³. Post-lactation, the decrease in prolactin and increase in estrogen levels initiate involution, which involves apoptosis of the alveolar cells and a reduction in breast size. The decline in estrogen levels during menopause results in a decrease in the size of the breast and an increase in fibrous tissue density, altering the shape of the breast ⁴.

2. BREAST CANCER

Breast cancer is a malignant proliferation of breast tissues arising in the epithelium of the ducts or lobules in the glandular tissue of the breast ⁵. It is a clinically, morphologically, and genetically heterogeneous disease. Breast cancer is classified based on histological subtypes, receptor status molecular subtypes, and tumor infiltration to the surrounding tissues ⁶.

2.1. Subtypes

Based on the level of tumor infiltration, breast cancers can be classified into in-situ or non-invasive carcinomas and invasive or malignant carcinomas ⁷. In-situ carcinomas are confined to the duct or lobule, are asymptomatic or mildly symptomatic, and have minimal potential for spread (metastasis). In-situ carcinoma can also be "pre-invasive," potentially invasive. In-situ carcinomas can be further subclassified into ductal or lobular based on their growth pattern. In invasive carcinomas, the cancerous cells infiltrate outside the lobules and ducts into breast tissues and spread to the nearby lymph nodes (regional metastasis) or other organs in the body (distant metastasis) ⁵. Invasive carcinomas are the most common type of breast cancer, comprising 70-85% of all breast cancers ⁶. The invasive tumors can be classified into over 20 different sub-classifications, with the most frequent being invasive lobular and infiltrating ductal carcinomas. Infiltrating ductal carcinomas represent 70-80% of all invasive breast cancers, whereas invasive lobular carcinomas comprise 10% ⁸.

In the majority of breast cancer cases, the tumors show biological expression of receptors for estrogen and progesterone, hormones that are known to promote the growth and proliferation of the tumor cells ⁹⁻¹¹. These hormones attach to the receptors in or on the cells and help the cancerous cells to grow ¹². Human epidermal growth factor 2 (HER2) is a membrane tyrosine kinase, and its amplification is essential in the pathogenesis and progression of breast cancers ¹³. Based on the expression of the hormone receptors and HER2, the tumor can be primarily classified into 4 subgroups. ^{14,15,16}.

- i) Luminal A subtype: characterized by the estrogen receptor-positive (ER+) and/or progesterone receptor positive (PR+), and human epidermal growth factor receptor negative (HER2-),
- ii) Luminal B subtype: characterized by the estrogen receptor-positive (ER+) and can be progesterone receptor positive (PR+),
- iii) HER2 subtype: human epidermal growth factor receptor positive (HER2+), and
- iv) Triple-negative (TNBC): characterized by the lack of expression of any of the above receptors

The expression of ER and PR receptors is crucial for diagnosing and determining targeted therapies for breast cancers. Approximately 70-75% of invasive breast carcinomas have high ER expression, and 50% of ER-positive carcinomas are also PR-positive. The overexpression of HER2 is found in 15-25% of breast cancer. The expression also plays a crucial role in choosing the targeted therapy. Luminal A type breast cancers are clinically low grade, low growing, and have a better prognosis, while Luminal B subtypes are high grade and have a worse prognosis. Luminal A and B are the most common types of tumors, comprising 60-70% of all breast tumors. The overexpression of HER2+ correlates with worse clinical outcomes and shorter disease-free periods¹⁵. Triple-negative breast cancer constitutes 20% of all breast cancers and is also typically associated with worse survival and higher rates of metastasis.

2.2. Clinical presentation, diagnosis, and screening

The most common presenting symptom of breast cancer is a lump or a mass in the breast or surrounding area. The early stages of breast cancer can be asymptomatic. Breast cancer can have a combination of many other symptoms, including swelling of all or part of the breast, breast or nipple pain, skin dimpling nipple retraction, nipple discharge, dryness/flaking/thickening of the skin on the breast or nipple, and swollen lymph nodes under the arm or near collar bones¹⁷.

Many of these symptoms can be associated with benign breast conditions. A breast lump can be evaluated through a physical exam, mammogram, and breast ultrasound¹⁸. An MRI can be performed in women with a high risk of breast cancer, with a personal or family history of breast cancer, or with dense breasts¹⁸. When mammograms, imaging, or physical exams

indicate the possibility of breast cancer, a breast biopsy is performed to confirm the diagnosis of breast cancer.

The diagnosis of breast is often facilitated by a routine screening, which aids the early detection and treatment, resulting in better outcomes. Screening methods include a physical breast examination, mammography, ultrasonography, and MRI¹⁹, among which mammography is a current gold standard for breast cancer screening. Screening with mammography has been found to reduce breast cancer mortality²⁰. For women with a higher risk of developing breast cancer, an MRI, in addition to annual mammography screening, is usually recommended¹⁹. In France, women aged 50 to 74 are recommended to have a mammography screening every two years²¹.

2.3. Grading and staging

After diagnosis, based on size, growth, and metastasis, using biopsies and other imaging methods, the tumors are differentiated into varying grades and stages¹⁹. Grading and staging are crucial for selecting appropriate treatments. Tumor grade refers to the appearance of cancer cells compared to other healthy cells and their likelihood to grow fast and spread. Breast tumors can range from low grade to high grade. Low-grade tumors have a uniform appearance and slow growth; intermediate-grade tumors are larger with variable shape and faster growth than normal cells, whereas high-grade tumors have different sizes and shapes than normal cells and are faster growing¹⁹.

The Tumor-Node-Metastasis (TNM) system is the most frequently used grading system that characterizes the tumors based on size (T), involvement of the lymph nodes (N), and spread to other tissues (M- metastasis)²². This system classifies the tumor into 5 stages, from 0 to IV. Stage 0 is non-invasive cancer, ductal carcinoma in situ, or Paget's disease without nodal involvement or distant metastasis. At stage I, the tumors are usually small (≤ 20 mm) with possible involvement of tiny lymph nodes, also known as micro-metastasis. Stage II involves larger tumors of up to 50mm, potentially involving nearby lymph nodes. Stage III tumors are more advanced and are of varying sizes with possible extension to the chest wall or skin with significant lymph node involvement. Stage IV tumors are those of any size with a distant metastasis and are the most advanced stages²².

2.4. Treatment, prognosis, and survival

Treatment for breast cancer is usually a varying combination of chemotherapy, radiation therapy, surgery, hormonal therapy, and biological therapy depending on the type, stage, hormone receptors, histologic markers, metastasis, menopausal status, age, other co-morbidities, and choice of the patients¹⁸. Breast cancer surgery is primarily of 2 types: breast-conserving surgery (BCS) and mastectomy. BCS is also called segmental mastectomy, which involves the removal of cancerous tissues while preserving the intact breast tissue²³. Mastectomy, on the other hand, is a complete removal of the breast and is often accompanied by immediate reconstruction²³. Hormonal therapies and chemotherapies combine various drugs administered based on the hormone receptor status, HER2 status, tumor size, metastasis, and reoccurrence¹⁸. Radiation therapy uses high doses of radiation to destroy the cancerous cells, usually administered after surgery or chemotherapy to minimize the possibility of breast cancer reoccurrence²³. Biological and targeted therapies use drugs most commonly to treat HER2-positive breast cancers²³.

Breast cancer prognosis often depends on the tumor stage, grade, size, hormone receptor status, HER2 status as well as age at diagnosis. Women diagnosed before 40 or after 60 frequently have poorer prognosis^{24,25}. According to the National Cancer Institute, the overall relative 5-year survival rate is 90.8%, varying by stage and subtypes²⁶. The 5-year net survival rate in France is 87% and 76% at 10 years²⁷. Relapse rates for breast cancer also vary by subtypes, with HER2 and triple-negative breast cancer showing higher local and regional reoccurrence, 7.5 and 3.4% for HER2 and 7.6 and 3.3% for triple-negative¹⁵.

3. EPIDEMIOLOGY OF BREAST CANCER

3.1. Incidence and mortality worldwide

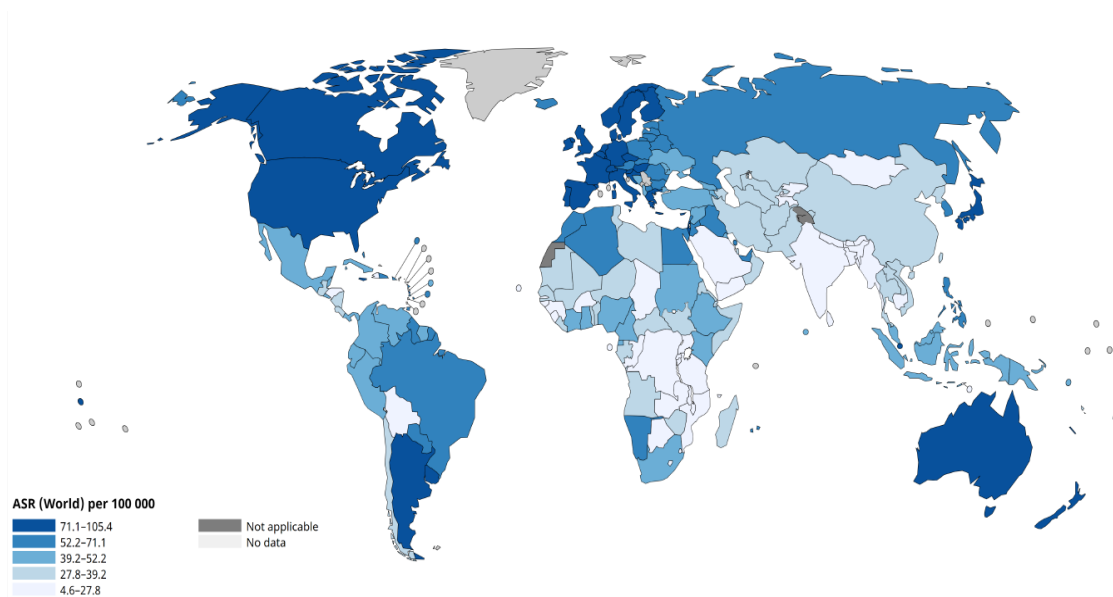


Figure 2: Age-standardized incidence rates in females due to breast cancer in 2020, Source: Cancer Today, IARC ²⁸.

Breast cancer is the most frequently diagnosed cancer and the leading cause of death among women worldwide ²⁹. In 2020, there were 2.3 million new cases of breast cancer worldwide, accounting for 12% of all new cancer cases among both sexes and 24.5% of all new cancer cases among women only. The deaths attributable to breast cancer in 2020 were 685,000 deaths, accounting for 7% of all cancer deaths in both sexes and 15.5% of all cancer deaths in women ³⁰. The world age-standardized incidence rate in 2020 was 47.8 per 100,000 person-years, while the age-standardized mortality rate was 13.6 per 100,000 person-years ³¹. Breast cancer incidence and mortality patterns vary widely across the countries. Breast cancer remains the most frequent cancer among women in all geographical regions and is a leading cause of death in Europe and Africa, while in America, Asia, and Oceania, it is the second leading cause of death among women ³¹. The highest proportions of new cases were diagnosed in Asia (49%), Europe (22%), and America (21%), and the highest mortality was also recorded in Asia (49%), Europe (22%), and America (21%) ³¹.

The distribution of age-standardized incidence rates across the countries shows significant geographical variability (Fig 2). The highest age-standardized incidence rates are observed in high-income countries such as France (105.4 per 100,000 person-years), Cyprus (104.8),

Belgium (104.4), and the Netherlands (101.6), whereas the lowest incidence rates were reported by low-income countries like Bhutan (4.6), Sierra Leone (7.0), and the Republic of Gambia (12.1) ²⁸. Higher incidences of breast cancer in high-income countries are potentially due to the longstanding higher prevalence of lifestyle and reproductive and hormonal factors, as well as advanced screening methods ³². However, the distribution of mortality rates showed a contrasting pattern with high mortality in less developed African countries and lower mortality rates in more developed countries (Fig 3) ²⁸. The highest mortality rates were reported in Barbados (42.2 per 100,000 person-years), Fiji (41.0), and Jamaica (34.1) ²⁸. In low and middle-income countries, insufficient services for cancer prevention screening, diagnosis, and treatment result in a frequent presentation at advanced stages, meaning poorer prognosis and higher mortality. Of note, the highest incidence rates were observed in countries with high Human Development Index (HDI) (75.7) and lowest in countries with low HDI (27.8); on the contrary, the death rates are highest in low HDI countries (13.6) and the lowest in high HDI countries (12.1) ³².

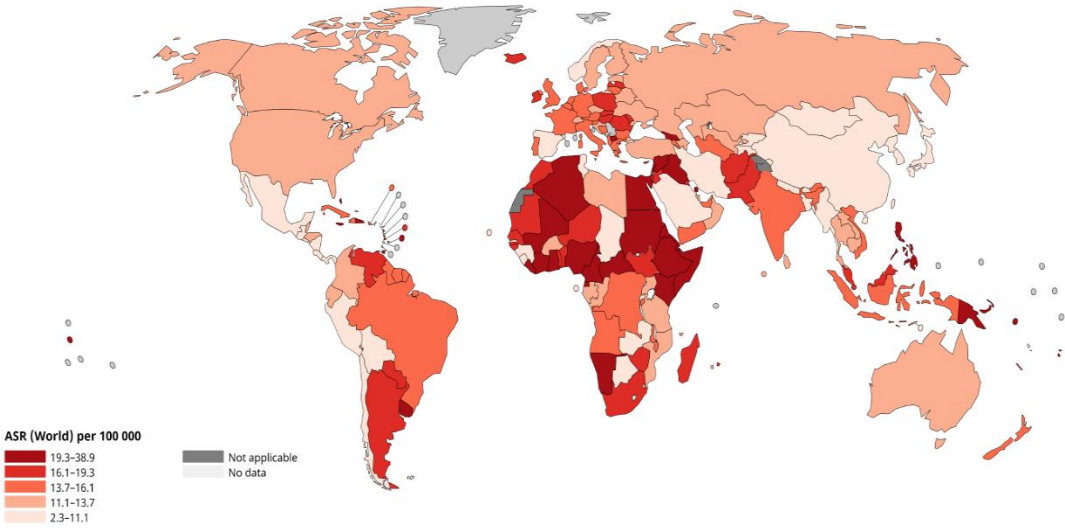


Figure 3: Age-standardized mortality rates in females due to breast cancer in 2020, Source: Cancer Today, IARC ²⁸.

Over the past three decades, the worldwide burden on women due to breast cancer has increased, especially among women aged 50-74 years ³³. Increasing trends in incidence rates have been observed in many countries, especially in transitioning countries, whereas mortality rates show a declining trend in many countries, especially in high-income countries ³⁴. Lowering mortality rates in high-income countries can be attributable to advancements in

treatments and better prognoses, while in several low and middle-income countries, an increasing trend in mortality rates can be due to women being diagnosed at advanced stages and inadequate treatment services ³⁴.

Breast cancer is estimated to increase to over 3 million new cases and 1 million deaths in the next 2 decades ³². Based on the growth and aging of the current population, by 2040, the incidence rates of breast cancer are estimated to increase by 40% worldwide, 30% in high HDI countries, and 97% in low HDI countries, while the mortality rates are projected to augment by 52% worldwide, 54% in high HDI countries and 99% in low HDI countries ³².

3.2. Incidence and mortality in France

In France, breast cancer remains the most common cancer and the leading cause of death among women, with 61,000 new cases and 12,000 deaths in the year 2023³⁵. The age-standardized incidence rate in 2022 was 105.4 per 100,000 person-years, while the mortality rate was 15.8 per 100,000. Breast cancer incidence in France is the highest in Europe, whereas France’s mortality rate stands at 14th rank in the region ²⁸.

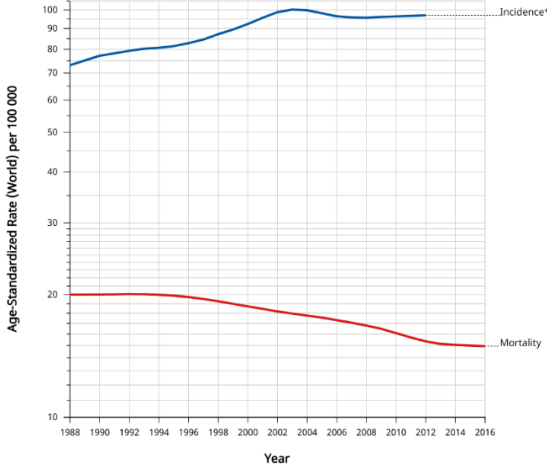


Figure 4: Trends in Incidence and Mortality rates in France from 1988-2016, Source: Cancer Over Time, IARC ³⁸.

The incidence rate has been rising since 1990, with variations in the period 2000-2009 (Fig 4) due to more organized screening and changes in hormonal replacement therapies for menopausal women. A moderate increase was seen in 2010-onwards, with an increase of 0.3% annually from 2010 to 2023 ³⁵. This increasing trend in France could signify a lasting trend and be linked to several lifestyle-related factors like alcohol and smoking, along with reproductive

and hormonal factors. The breast cancer mortality rate steadily decreased with a 1.3% reduction annually from 1990 to 2018 ^{36,37}. Advancements in treatment methods, improved screening, and early diagnosis could explain this decreasing trend.

Breast cancer incidence rates in France exhibit a scattered distribution across departments, with the highest rates being more frequently observed in the northern, southern, and western departments (Fig 5) and the highest mortality rates observed predominantly in northern departments.

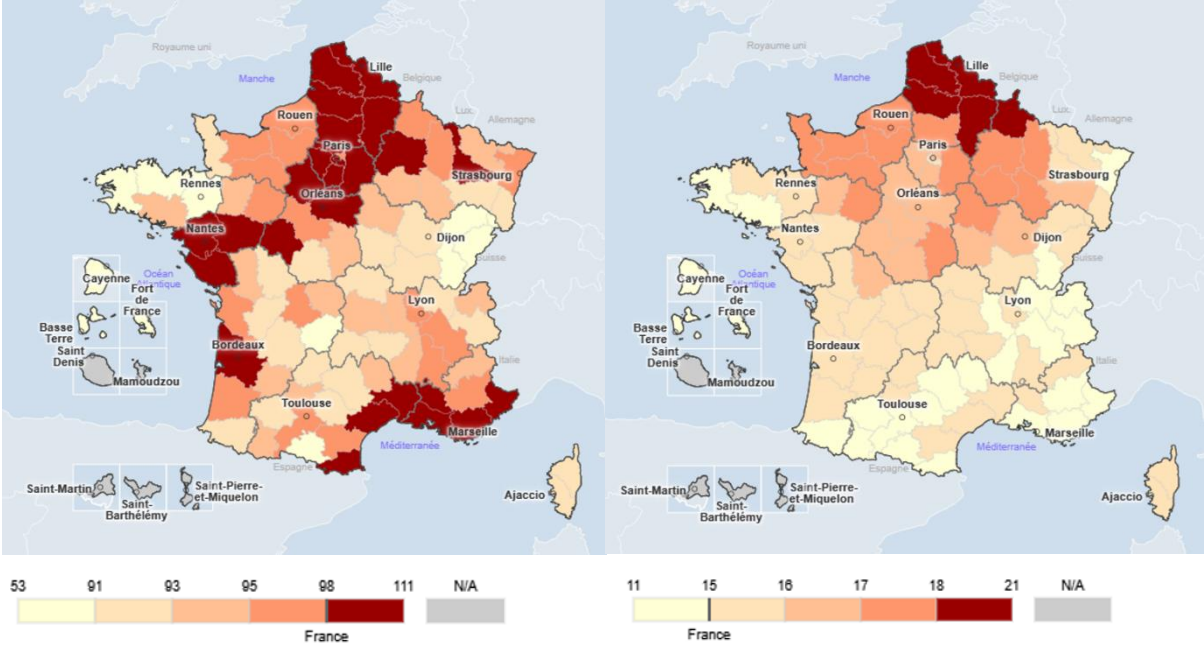


Figure 5: Standardized incidence (left) and mortality ratios (right) for breast cancer in women by departments in metropolitan France 2007-2014 ³⁸.

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4. RISK FACTORS

Breast cancer is a heterogeneous disease with a multifactorial causation. Numerous modifiable and non-modifiable risk factors have been recognized to be associated with an increased risk of breast cancer. Breast cancer is a hormone-sensitive cancer; several risk factors work through hormone-dependent mechanisms. Due to changes in the development and function of breasts, hormonal changes throughout life, and reproductive functions, females are primarily at risk of developing breast cancer ^{5,23}.

4.1. Age

The risk of breast cancer increases with increasing age ²³. The median age at diagnosis in France is 64 years ³⁹. The risk is often higher among women of older age (>40 yrs) ^{40,41}. The majority of breast cancer cases (80%) are diagnosed in women >50 years of age, and 40% of them are among even older women >65 years ²³. The majority of invasive breast cancer cases occur among women over 50 ⁴². The triple-negative breast cancer subtype is commonly diagnosed in women younger than 50 years, while the Luminal A subtype seems to be the most common among older women (>70 years) ⁴³. Older age can signify numerous cellular changes, the accumulation of exposure to multiple carcinogens and other co-morbidities, and thus increases the risk of breast cancer with potentially poorer prognosis.

4.2. Heredity and genetics

4.2.1. Family history of breast cancer

The risk of breast cancer is significantly higher among women with a family history of breast cancer compared to the general population ⁴⁴. The risk depends on many factors such as the number of relatives and their generational distance, age of diagnosis of the relatives, history of ovarian cancer and other cancers, genetic mutations, etc. Having one first-degree relative with breast cancer doubles the risk and increases further with more affected relatives ⁴⁵. The risk is notably higher if the relative's diagnosis is <50 years or before menopause ⁴⁴. A family history of ovarian cancer in conjunction with breast cancer can increase the risk of breast cancer as both can be linked with the same genetic mutations of BRCA1 and BRCA2 ^{46,47}. Besides, a family history of breast or other cancers can also indicate a predisposition to shared environmental or lifestyle-related exposures over time.

4.2.2. Genetic mutations

The BRCA1 and BRCA2 are tumor suppression genes crucial for repairing DNA damage and maintaining cellular stability ⁴⁸. Mutation in these high-penetrating genes can lead to an impairment of their ability to regulate cancer development and promote breast carcinogenesis ⁴⁹. The mutations in BRCA1 (located in chromosome 17) and BRCA2 (located in chromosome 131) are responsible for 5-10% of total breast cancer cases ^{50,51}. These mutated genes can be inherited from the parents and transferred to the following generation ⁴⁸. Women who carry these mutated genes have an 85% lifetime risk of developing breast cancer ⁴⁸. Among women who carry the BRCA1 mutation, the 10-year cumulative risk of breast cancer was 18.1%, while for women carrying a BRCA2 mutation was 15.2% ⁴⁷. Most of the carriers of these genetic mutations are diagnosed at a younger age (<50 years) ⁵². Besides these significant 2 genes, other high penetrating genes such as TP53, CDH1, PTEN, STK11m, and other moderate and low penetrating genes are usually linked with breast carcinogenesis ^{23,49}.

4.3. Hormonal and reproductive factors

Over a lifetime, physiological changes and specific events such as menstruation, pregnancy, lactation, and menopause result in varying levels of estrogen and progesterone, the hormones that are mainly linked with increased risk of breast cancer ^{53,54}. Several reproductive and hormonal factors are established as prominent risk factors for breast cancer.

4.3.1. Age at menarche and menopause

Menarche and menopause are major biological events in a woman's life, indicating the onset and cessation of ovulatory hormonal activities. Earlier age at menarche and a later age at menopause is associated with a higher risk of breast cancer ⁵⁵⁻⁵⁷. A pooled analysis of 117 epidemiological studies showed that the risk increases by 5% for every year younger at menarche and 3% for every year older at menopause ⁵⁸. In the E3N-Generations cohort, the cumulative numbers of menstrual cycles were found to be associated with an increased risk of breast cancer ⁵⁵. The same study reported twice as high risk of breast cancer for menopause after the age of 55 years compared to before 40 years, also showing an increasing risk for increasing age at menopause. Younger age at menarche and older age at menopause suggest more menstrual activity and a prolonged lifetime exposure to estrogen in a woman's body, which in turn can increase the risk of breast cancer ⁴⁸.

After menopause, the production of estrogen and progesterone varies. Menopausal status is also considered an important factor in breast cancer risk due to varying hormonal activities along with other physiological and lifestyle changes. While the age-specific incidence rises exponentially until menopause and rises steadily afterward ⁴², mortality is observed to rise rapidly after 60 years ⁵⁹.

4.3.2. Pregnancy and Parity

Pregnancy reduces a woman's lifetime exposure to estrogen and the total number of menstrual cycles, factors that are linked to breast cancer risk. Women who have their first full-term pregnancy at a younger age have a lower risk of breast cancer ⁵⁶. A pooled analysis, including 20 studies, reported that the risk increases with age at the first full-term pregnancy ⁵⁵. This pooled analysis also showed that for every year added at first full-term pregnancy, the risk increases by 5% for pre-menopausal breast cancer and by 3% for post-menopausal breast cancer ⁵⁵. An early full-term pregnancy leads to an early maturation of mammary glands, a higher degree of cell differentiation, and reduced cell proliferation ⁶⁰.

Parity has been reported to have a bifurcating effect on breast cancer risk with short-term increase and long-term reduction of the risk. Within 5 years of delivery, there is a short-term increase in risk, possibly due to hormonal stimulation and proinflammatory stimuli during wound healing ⁵². Being nulliparous increases the risk more than 3 folds (OR: 3.77, 95% CI: 1.98-7.30) compared to parous women, according to a Moroccan case-control study ⁵⁶. However, with increasing parity, the risk usually decreases ⁵⁵. With each parity, the risk for premenopausal breast cancer reduces by 3% and by 12% for postmenopausal breast cancer ⁵⁵. Multiple parity, overall, reduces the cycles of menstruation, thus reducing the lifetime exposure to estrogen, also resulting in breast cell differentiation, making the breast cells less susceptible to carcinogenic changes ⁶⁰.

4.3.3. Breastfeeding

Breastfeeding is consistently reported as a protective factor against breast cancer, with increasing effects for increasing duration of breastfeeding ⁶¹. During lactation, there is a delay in ovulation, which results in fewer ovulatory cycles and, thus, lesser lifetime exposure to estrogen. A pooled result from 20 epidemiological studies showed that breastfeeding for 3 months and more results in a 16% reduction in breast cancer risk compared to parous women

who never breastfed⁵⁵. Another meta-analysis of 47 studies from 30 different countries demonstrated that for every 12 months of breastfeeding, there is a risk reduction of 4.3%⁶¹. Regardless of the duration of breastfeeding, ever breastfeeding has also been associated with a reduced risk for luminal subtype and triple-negative breast cancers by 23% and 21%, respectively⁶². However, it is also an important modifiable factor and occasionally a lifestyle choice of women, especially in high-income countries, pertaining to multiple factors⁶³. Along with other significant lifestyle changes, lower breastfeeding practices in high-income countries have partially contributed to high incidences of breast cancer⁶³, and a substantial proportion of the cumulative incidence in these countries could be minimized by more prolonged duration of breastfeeding⁶¹.

4.3.4. Oral contraceptives use

Oral contraceptives are synthetic hormones usually available as combined estrogen-progesterone or progesterone-only forms. The working group of the International Agency for Research on Cancer (IARC) evaluated the benefits and risks of oral contraceptive use and concluded that combined oral contraceptives are carcinogenic to humans based on an increased risk for breast and ovarian cancer⁶⁴. Use of oral contraceptives for a longer duration, starting at a younger age before the first full-term pregnancy, is reported to have a more significant impact on increased breast cancer risk⁶⁵ possibly because the breast cells are less differentiated before the pregnancy and thus increases the chances of proliferation due to the hormones⁵⁴. An analysis from the Collaborative Group on Hormonal Factors in Breast Cancer using 54 epidemiological studies demonstrated that the current users of combined oral contraceptives had a 24% increase in breast cancer risk compared to never users, with the risk diminishing after 10 years of discontinued use⁶⁶. A recent meta-analysis also concluded from 42 prospective cohort studies that ever use of oral contraceptives was positively associated with breast cancer risk⁶⁷.

4.3.5. Menopausal hormonal therapy

Menopause signifies the cessation of cyclic ovarian hormone production, resulting in many physiological changes. Menopausal hormonal therapies (MHT) are thus provided to post-menopausal women to supplement the loss of hormones during the transition and to alleviate the symptoms associated with menopause⁶⁸. Heightened risk is usually linked with MHT use

and a longer duration of its use among postmenopausal women ⁵². A reanalysis of 51 epidemiological studies in 1997 indicated a 2.3% increased risk of breast cancer associated with MHT. After the cessation of MHT, this risk starts to diminish and significantly reduces after five years ⁶⁹. A more recent meta-analysis of 62 prospective cohort studies in 2021 demonstrated a pooled estimate of 1.26 (95% CI: 1.20-1.32) for ever-using MHT ⁶⁷. The Women's Health trial that started in 1998 published the results in 2002 stating that MHT increased the incidence of breast cancer, which led to the recognition of MHT as a risk factor for breast cancer, along with a subsequent rapid decrease in MHT use among postmenopausal women ^{70,71}.

4.4. Lifestyle-related factors

4.4.1. Body-Mass Index

BMI has been consistently reported to be associated with breast cancer risk. A meta-analysis including 12 studies showed that for every 5 kg/m² there is a 25% increase in overall breast cancer risk ⁷² however, BMI had a different effect based on menopausal status ⁷³⁻⁷⁶. A higher BMI could be a protective factor in pre-menopausal women but a risk factor in postmenopausal women ⁷³⁻⁷⁶. A pooled study using data from 758,000 pre-menopausal women demonstrated a four-fold reduction in risk among women with the highest BMI compared to those with the lowest BMI at 18-25 years old. ⁷⁷. A 34-studies meta-analysis reported a 12% increase in the risk of breast cancer for every 5kg/m² increase in BMI among postmenopausal women ⁷⁸. A higher BMI makes postmenopausal women more susceptible to developing ER/PR-positive breast cancer ⁷⁹ as well as larger, advanced, and highly metastatic tumors ⁸⁰.

The differential effects of BMI in pre and postmenopausal women are associated with hormone-dependent mechanisms. A higher BMI at a younger age could result in higher estrogen and early breast cell differentiation, resulting in less proliferation ⁷⁷. In postmenopausal women, the adipose tissues become the primary source of estrogen production, and despite the cessation of cyclic ovulatory estrogen production, circulating estradiol becomes higher with increasing BMI, which increases the risk of breast cancer ⁶⁹.

4.4.2. Physical activity

Sufficient physical activity levels are among several significant lifestyle-related factors that protect against breast cancer risk ⁷⁶. Studies have reported that no or insufficient physical activity increases breast cancer risk ^{81,82}. A meta-analysis based on 16 studies demonstrated, with a pooled estimate of 0.90 (95% CI: 0.86, 0.95), that at least 30 minutes of moderate to vigorous physical activity per day is associated with lower risk of breast cancer ⁶⁷. The Women Health Initiative Cohort study involving 74171 women aged 50-79 reported a lowered risk of post-menopausal breast cancer associated with increased physical activity ⁸³. The same study also depicted that regular strenuous physical activity at age 35 lowers the risk of breast cancer by 14%, with a longer duration of physical activity having a more pronounced reduction in the risk ⁸³. Among several mechanisms behind this protective effect of higher physical activity against breast cancer risk, some are reduction of fat tissue obesity management, regulation of sex hormones, especially estrogen, regulation of other metabolic hormones like insulin, and reduction of growth factor, all together lowering the risk of carcinogenesis ⁸⁴.

4.4.3. Alcohol consumption

A European Prospective Investigation into Cancer and Nutrition reported that the time of alcohol consumption can significantly affect the risk of breast cancer development such that alcohol intake before the first full-term pregnancy poses a higher risk ⁸⁵. This study also reported a varying risk for varying quantities of alcohol intake. Each 10-gr/day consumption caused a 2% increase in the risk, whereas an intake of 5-15 gr/day compared to 0-5 grams/day was associated with 5.9% ⁸⁵. A further reanalysis of 53 epidemiological studies showed that 35-44 gr/day resulted in a 32% increase, and more than 45 gr/day increased the risk to 46% ⁸⁶. Based on 56 studies, a metanalysis presented a pooled estimate of 1.10 (95% CI: 1.07-1.12) comparing ever-alcohol-consuming women to never ⁶⁷. Based on the evidence on several cancers, including breast cancer, in 2010, IARC classified alcoholic beverages as carcinogenic to humans (Group 1). The carcinogenic substances present in alcoholic beverages induce hormone alteration (increase in estrogen), suppress immune function, and inhibit DNA methylation ^{52,87}.

4.4.4. Smoking

Tobacco smoking in both active and passive forms has been suggested to be associated with breast cancer risk⁸⁸, yet the results are dividing. The Collaborative reanalysis of 53 epidemiological studies in 2002 showed that there was no association (RR: 1.03, 95% CI: 0.98-.07)⁸⁶, while a more recent meta-analysis of 90 studies in 2021 showed a positive association (RR: 1.07, 95% CI: 1.05-1.09)⁶⁷. Most recent evidence suggests a potentially causal role of active smoking for a long duration initiated at a younger age⁸⁸. Recent studies that have measured smoking behavior in a detailed manner using duration intensity, pack-years, age at initiation, etc., have provided more positive results⁸⁹ as compared to those using the crude measures of ever-never smoking status⁹⁰. Tobacco contains numerous carcinogenic chemicals that lead to DNA adduct formation, DNA mutation, and dysregulated signaling pathways of tumor-inhibiting genes, thus promoting cancer risk⁸⁹.

4.4.5. Diet

Diet is yet another essential lifestyle-related factor, suggested to be a risk factor for breast cancer with conflicting results. Evidence suggests that fatty diet, ultra-processed food, red meat consumption could increase breast cancer risk^{23,50,67}, while diets high in fruits, vegetables, whole grains, lean protein, etc., could confer a protective role against breast cancer^{23,67,91}. However, due to the diversity and complexity of the dietary composition and patterns, the estimation of the diet/nutrient-specific effect on breast cancer remains complicated.

4.4.6. Occupational factors

Occupational exposure to breast cancer risk is a long-studied issue. Occupational exposure comprises a mixture of factors in the occupational environment, such as ionizing and non-ionizing radiation, pesticides, aromatic hydrocarbons, metals, and other chemicals⁹². While some occupations that require physical activity are suspected to reduce the risk of breast cancer⁹³, other occupations that require night shift work are recognized to have increased the risk of breast cancer⁹⁴⁻⁹⁶. It is challenging to assess single occupational exposure in isolation due to the limited detailed exposure assessment methods⁹². Night shift work, classified as 'probably carcinogenic to humans (Group 2A)' by IARC in 2019⁹⁷, is discussed in detail in Chapter 1, section 7.

4.5. Environmental factors

4.5.1. Air pollution

Experimental studies provide evidence that the carcinogens present in ambient air pollution are linked with breast carcinogenesis⁹⁸. Some epidemiological studies reported that air pollutants, especially nitrogen dioxide (NO₂), particulate matter (PM_{2.5}, PM₁₀), and polycyclic aromatic hydrocarbons, are linked with a higher risk of breast cancer^{99,100}. A pooled analysis from 15 European cohort studies provided suggestive evidence of the association of breast cancer with long-term exposures to nitrogen dioxide, nitrogen oxides, and particulate matter⁹⁸. Other recent meta-analyses reported an increased risk of breast cancer due to increasing ambient air pollutants, specifically NO₂, a common traffic-related air pollutant¹⁰¹. The underlying mechanisms of breast carcinogenesis due to air pollutants involve the formation of DNA adducts, gene mutations, and several other molecular changes that facilitate the initiation and progression of breast tumors¹⁰².

4.5.2. Noise pollution

Among the environmental factors, exposure to noise pollution is a less frequently studied factor in breast cancer risk. Emerging evidence suggests a positive association between noise exposure and breast cancer risk. The Danish cohort study among 22,466 women reported a 10% increasing breast cancer incidence for each 10dB increase in noise level¹⁰³. Recent results from a pooled study of 8 Nordic countries indicate a weak association of breast cancer with road traffic and railway noise exposure¹⁰⁴, while another meta-analysis including 4 epidemiological studies reported a positive association¹⁰⁵, rendering a conflict in the results. The underlying mechanism for this inconclusive association is hypothesized to be sleep disruption, circadian disruption, and an increase in cortisol levels, potentially leading to immune suppression and promoting tumor progression due to prolonged noise exposure¹⁰⁴.

4.5.3. Proximity to green spaces

Research indicates a correlation between proximity to green spaces and reduced breast cancer risk¹⁰⁶. Only a limited number of studies have studied and reported that residential greenness¹⁰⁷⁻¹⁰⁹ and proximity to urban green spaces¹¹⁰ provides a protective effect against breast cancer. It is hypothesized that green spaces like parks and gardens near residential areas

promote physical activity, mental health, and social cohesion, as well as provide a physical barrier against outdoor exposures such as air pollution, noise, and outdoor light at night (LAN)^{106,111}. However, proximity to other green spaces, such as agricultural areas, farms, etc., might result in higher exposure to pesticides and other chemicals, possibly carcinogenic.

4.5.4. Urbanization

Urbanization itself is not a direct risk factor, yet the incidence rate of breast cancer is observed to be higher in high-income sub-urban areas¹¹². Studies have shown that being born and living in urban areas is linked with increased breast cancer risk^{113,114}. Living in an urban area could reflect a complex mix of exposures such as air pollution, noise pollution, reduced greenness, other environmental and occupational exposures, and varying socioeconomic status^{115,116} along with the exposure to artificial LAN (discussed in chapter 1 section 8).

5. CIRCADIAN RHYTHM, DISRUPTION, AND THE FUNCTION OF MELATONIN

Circadian (circa, "about" and diem "day") rhythms are endogenous oscillations with a periodicity of approximately 24 hours resulting from the interaction between the solar cycles (light-dark cycle or day-night cycle) and the body's internal circadian clock ¹¹⁷. This rhythm prepares and adjusts physiological functions according to the daily changes in the environment ¹¹⁸. The rhythm is generated by the suprachiasmatic nuclei (SCN) situated in the anterior hypothalamus, which serves as a central clock, the central oscillator, and the pacemaker for the rhythm ¹¹⁹. The SCN also regulates peripheral oscillators, which consist of networks of 'clock genes' that synchronize local timekeeping in various organs and tissues in the body ¹²⁰. The circadian rhythm, thus created, is entrained by the external environment predominantly through information on natural light-dark cycles and behavioral factors like sleep and activities ¹²¹. The light is perceived by the retina and sent directly to the central clock ¹¹⁹. The retina contains 2 types of photoreceptors: i) image-forming photoreceptors known as rods and cones, and ii) non-image-forming photoreceptors known as intrinsically photosensitive retinal ganglion cells (ipRGCs) ¹¹⁹. The visual and non-visual light perceived by the rod/cone cells and intrinsically ipRGCs sends signals to the master clock, the SCN ¹²². The SCN signals the peripheral tissues influencing several physiological functions in the human body such as sleep-wake, hunger, alertness, cognitive performance, blood pressure, temperature, metabolism, and hormone production and stimulation, and thus regulation of the rhythm is achieved ^{96,123,124}. The SCN also prompts the pineal gland to secrete melatonin hormone, often called the "sleep hormone" or "hormone of darkness." This hormone sends feedback to the SCN, helping further regulate the circadian rhythm ¹²⁵.

Light detected by the ipRGCs activates melanopsin, a unique photoreceptor involved in melatonin production, responding directly to light exposure ¹²⁶. Melatonin production is influenced by light; its secretion increases in the dark phase, promoting the sleep cycle. The secretion and peak level of melatonin varies within an individual over 24 hours, rising a few hours before sleep, peaking during sleep in the absence of light, and declining back in the morning ¹¹⁸. This pattern also maintains sleep-wake cycles and alertness. Increased light exposure reduces the circulating melatonin in the blood ¹²⁰ and interrupts the signal from SCN, resulting in the inhibition of melatonin secretion and delaying the nocturnal peak ^{119,122,124}. The

iPRGs, melanopsin, and melatonin production are susceptible to shorter wavelengths of light (~480 nm) and less to longer wavelengths (>600 nm)¹²⁶. Thus, with its shorter wavelength (~480 nm), blue light has the most inhibitory effect on melatonin production at night, often leading to a higher degree of circadian disruption¹²⁷.

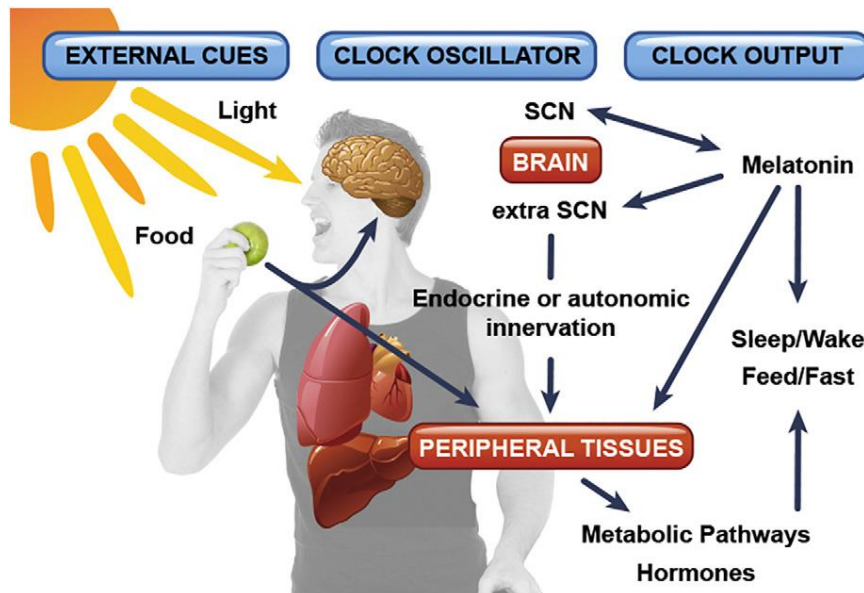


Figure 6: Regulation of circadian rhythm by internal and external cues¹²⁸.

Besides its role in circadian rhythm, melatonin is an immune regulator, a significant antioxidant, and an anti-inflammatory agent¹²⁵. It is also recognized for its oncostatic and tumor-inhibitory properties^{123,125}. Thus, disruption in melatonin release and circadian rhythm not only leads to sleep disturbances but also to a reduction in the oncostatic effect of melatonin, which may contribute to malignant proliferation of cells and enhance tumor development^{96,125}. Inhibition of melatonin secretion as a result of exposure to LAN also interferes with estrogen receptor function, affects free radical biology, and causes immunosuppression, thereby increasing the risk of breast cancer¹²⁹. Additionally, melatonin plays several inhibitory roles in cancer progression, showing the multifaceted importance of melatonin regulation (Fig 7).

Lifestyle-related factors such as leaving lights on at night, not using blinds or curtains, irregular sleep patterns, using electronic devices before bed, and living in areas with intense LAN can lead to increased exposure to both indoor as well as outdoor LAN¹²¹ which directly influence the circadian rhythm.

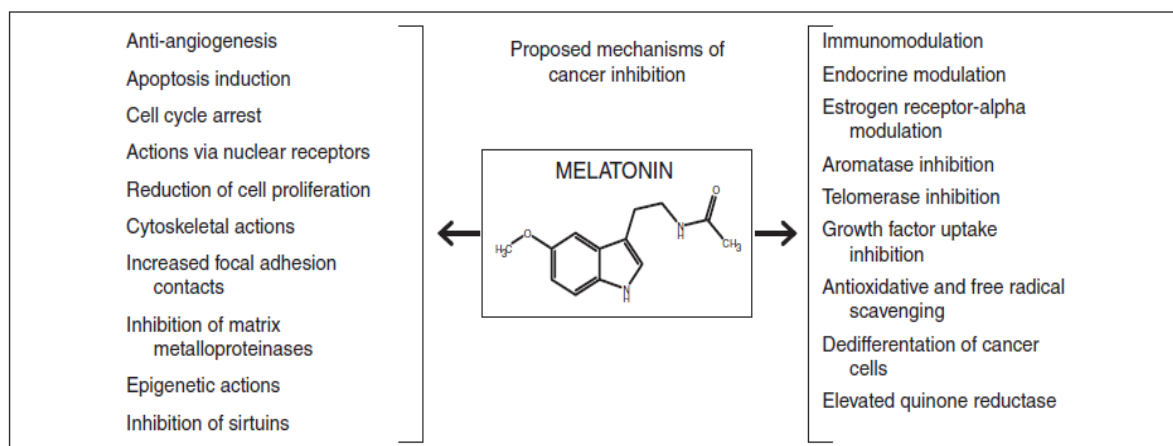


Figure 7: Mechanism behind melatonin's cancer inhibitory properties ¹²⁵.

A clinical trial analyzing melatonin profiles among healthy adults in Boston found that high exposures to light before bedtime delayed melatonin onset in 99% of individuals and shortened its duration by 90 minutes, while light exposure during sleep hours reduced melatonin by more than 50% ¹³⁰. Besides light, a primary cue for circadian rhythm, some non-photic cues, such as meals, exercise, work schedule, etc., can also alter this rhythm ¹²¹. While the circadian rhythm regulates the hunger cycle, irregular meal patterns can dysregulate this cycle ¹³¹. Occupations with night shift work, which involve prolonged indoor and outdoor exposure to light and irregular meal patterns that contradict the natural light-dark phase, also contribute to circadian disruption ⁹⁷. In 2019, the IARC concluded that "night shift work involving circadian disruption" is probably carcinogenic to humans (Group 2A) based on limited evidence from human studies and sufficient evidence from animal studies ⁹⁷ (See Chapter 1 section 7).

Misalignment between social time and the biological clock caused by travel, jetlag, and social events can also temporarily alter the circadian rhythm ¹¹⁷. Genetic variations in 'clock genes' also influence individual differences in the rhythm and synchronization with the environmental cues. These genetic differences result in a range of chronotypes reflecting the unique alignment of each individual's internal circadian clock to external cues ¹¹⁷. Chronotype defines an individual's diurnal preferences for either morning or evening activity ¹¹⁷. It could modify the risk of cancer due to circadian disruption by influencing individuals' adaptability to misalignments in schedules and biological clocks ¹³². Chronotypes have also been reported to be linked with varying risks of breast cancer ^{133,134}.

5.1. Health effects of circadian disruption

Disruption in circadian rhythm is linked with multiple detrimental health effects ¹²¹. This disruption can lead to metabolic dysfunctions such as decreased insulin sensitivity and an increase in energy intake, leading to metabolic disorders like type 2 diabetes ¹³⁵. Additionally, circadian misalignments may disturb the normal rhythms of cortisol and other stress hormones, elevate blood pressure, and reduce heart variability, thereby increasing the risk of cardiovascular diseases ¹³⁵. Elevated inflammatory markers such as c-reactive protein (CRP) and interleukin-6 (IL-6) have also been associated with disruptions in circadian rhythm ¹³⁵. Furthermore, circadian disruptions may also cause imbalances in leptin and ghrelin, hormones that regulate hunger and satiety, which lead to the uptake of sugary or fatty food during the periods of circadian misalignment, especially at night, disrupting normal fasting period and increasing the risk of weight gain ¹³⁵.

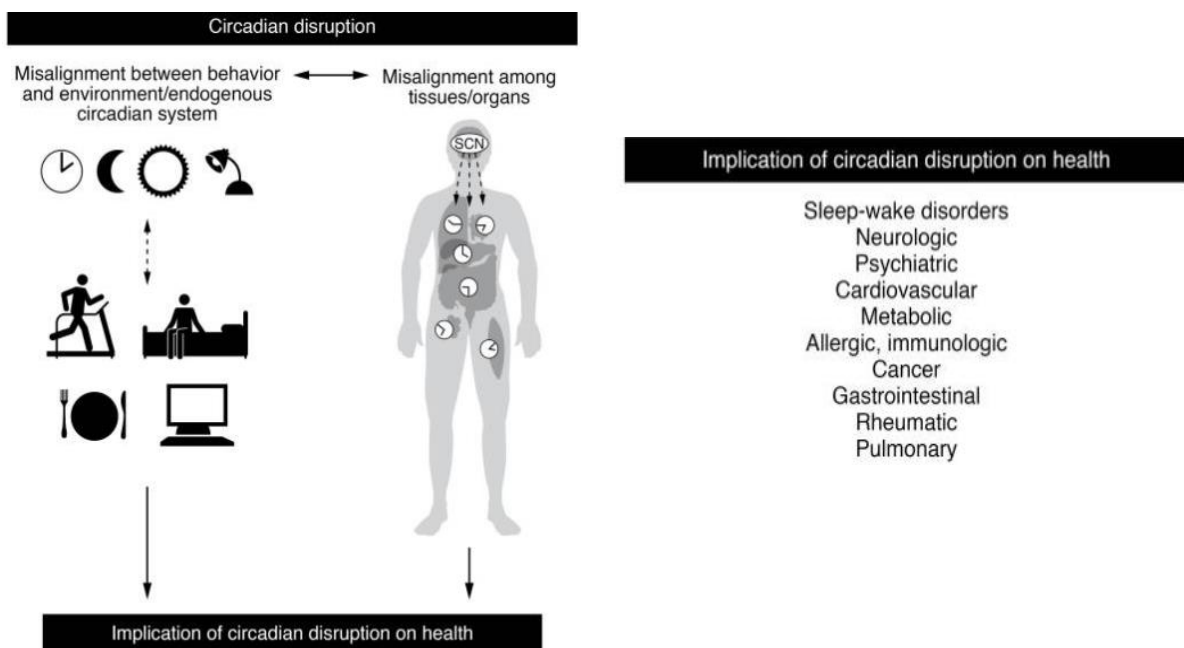


Figure 8: Inter-relationships between circadian disruption and human health ¹²¹.

Disruptions in sleep cycles have also been associated with cognitive deficits such as impaired memory, decreased attention span and slower reaction time, mood disorders, and impaired emotional regulation ¹³⁵. Studies have also suggested that circadian-disrupting behaviors such as exposure to LAN, night shift work, and sleep dysregulation are positively associated with an increased breast cancer risk ¹³⁶.

6. MEASURING CIRCADIAN DISRUPTION IN EPIDEMIOLOGICAL STUDIES

Circadian rhythm functions from molecular to behavioral level, and its disruption leads to a range of biological and behavioral changes. Several biological markers and behavioral and lifestyle factors have been associated with circadian rhythm and can serve as indicators for assessing circadian disruption. Typical measures used in experimental studies to assess the extent of circadian disruption are melatonin or cortisol levels or core body temperatures. In contrast, in observational studies, levels of physical activity, chronotype, variation in sleep timing, shift work, artificial light at night, and so on are measured ¹³⁷.

Measuring circadian disruption in epidemiological studies is challenging as it would require a long-term exposure assessment in a sufficiently large population to yield robust data and reliable results ¹³⁷. Direct measurement of biological markers such as melatonin levels or body temperatures is not feasible in large-scale studies due to logistic and financial constraints. Therefore, night shift work or exposure to light at night can serve as reasonable proxies to measure the potential chrono-disruption. Since light acts as one of the primary cues for circadian rhythm, and the elements in night shift work, such as altered activity alertness, activity levels, sleep, and meal schedules ¹³⁸, can provide an indirect yet practical means of assessing circadian disruption in large epidemiological studies.

Several epidemiological studies have attempted to assess the effects of circadian disruption on breast cancer risk by measuring varying aspects of behavior and lifestyle, including type of occupation such as shift work, flight attendants, exposure to LAN, etc. A meta-analysis including 28 studies that assessed different circadian disrupting exposures such as shift work, LAN, sleep disruption, or working as flight attendants, has reported a positive pooled estimate (RR: 1.14, 95% CI: 1.08-1.21) for breast cancer risk and circadian disruption ¹³⁹.

Research on circadian disruption has focused primarily on shift work that involves night shifts, which have been extensively studied in observational studies ¹³⁷. Meta-analyses of studies using night shift work as a proxy for circadian disruption have demonstrated a positive association with breast cancer ¹⁴⁰ while individual studies have noted a similar association of night shift work with prostate cancer ^{132,141}. In 2007, IARC classified "shift work that involves circadian disruption" as "probably carcinogenic to humans" (Group 2A) and reconfirmed the classification in 2019 based on sufficient evidence from animal studies and limited evidence

from human studies ⁹⁷. It suggested that the potential carcinogenic mechanism linked to night shift work stems from the desynchronization between the external light-dark phases with the endogenous circadian rhythm due to exposure to artificial LAN, changes in activity levels, alertness, cognitive function, and meal schedules caused by the night shift schedules ⁹⁷.

Epidemiological studies on LAN exposure and breast cancer risk have been relatively recent and with a rise in interest from the scientific community in recent decades. While night shift work offers a measure of circadian disruption through composite behavioral and environmental aspects, it is relevant only to a specific population group involved in occupations such as health care, security professionals, hospitality, or construction. However, due to the widespread access to electric light and transformation into a 24-hour society, the impact of LAN extends beyond shift workers. The pervasive impact of LAN has gained significant attention in the scientific community, resulting in a transition from focusing predominantly on shift work to assess circadian rhythm to using exposure to outdoor LAN as a proxy for circadian disruption.

Although night shift work and exposure to artificial LAN offer distinct perspectives on circadian disruption, both are crucial to be measured because they reflect the diverse environmental and behavioral influences that can significantly elevate breast cancer risk in varied segments of the population. Therefore, it is in this context that this thesis will study circadian disruption measured through exposure to outdoor LAN and night shift work and its role in breast cancer risk. The following sections will detail on night shift work and LAN, along with the review of available literature on both exposures and their association with breast cancer risk.

7. NIGHT SHIFT WORK

Earlier in the industrial era, non-standard shifts extending beyond 8 am and 4 pm were introduced to keep the factories and manufacturing plant running 24 hours¹³⁸. Modern societies today are characterized by a fast-paced rhythm of production and consumption of goods and services, which also necessitates continuous operation and production around the clock. This need for continuous production of services enables atypical work schedules such as shift work, night work, part-time work, and weekend work¹⁴². Currently, approximately only one-fourth of the global workforce has regular day schedules¹³⁸. Non-standard working hours are prevalent in essential service sectors, including healthcare, transportation, communication, security, law enforcement, and hospitality¹⁴³. Within this evolving global workforce, night shift work has become a fundamental component of industrial and service economies, facilitating 24-hour activities across various sectors. Shift work and its impact on human health has been widely studied and has been recognized to have a wide range of impacts, such as cardiovascular and metabolic dysfunction, sleep disorders, increased cancer risks, and anxiety and depressive disorders, among other health concerns¹⁴⁴. The alteration in work patterns necessitating various physiological and behavioral adaptations has significant implications for workers' health, particularly those concerning circadian rhythms¹³⁷. Night shift work that disrupts natural circadian rhythms can potentially lead to various health issues, including an increased risk of cancer.

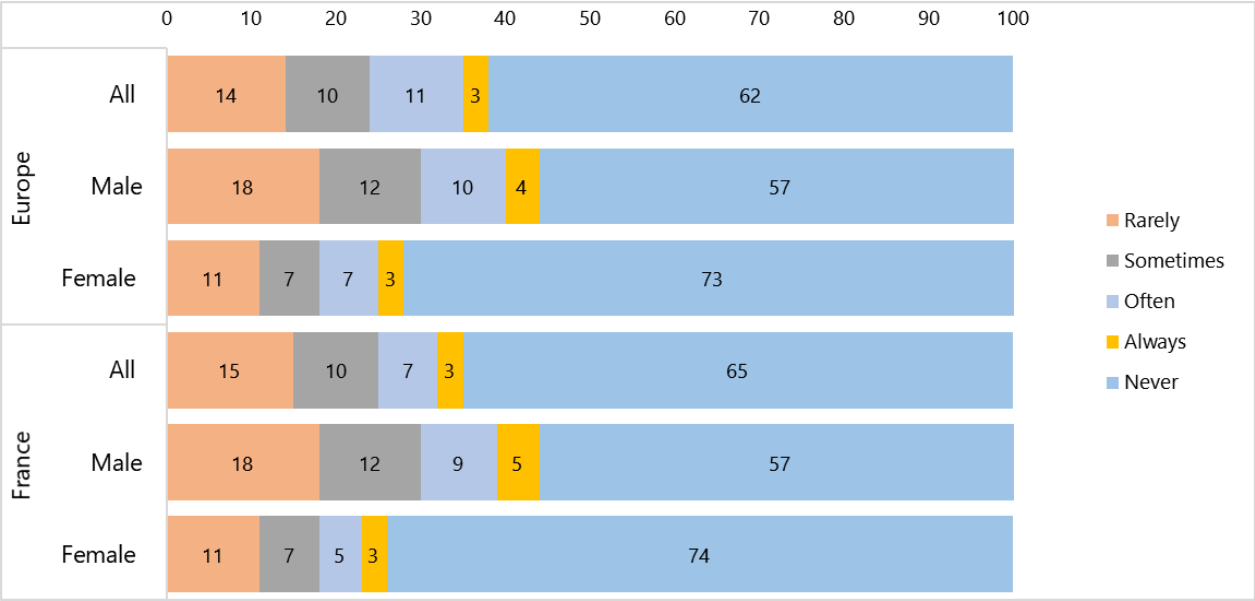
The IARC Monograph on Night Shift Work (Volume 124) provided a comprehensive evaluation of the carcinogenic risks associated with night shift work based on the review of experimental and epidemiological studies. In 2007, IARC classified "shift work that involves circadian disruption" as "probably carcinogenic to humans" (Group 2A). In 2019, the classification was reconfirmed based on sufficient evidence from animal studies and limited evidence from human studies⁹⁷. IARC's monograph suggested that the potential carcinogenic mechanism linked to night shift work stems from the desynchronization between the external light-dark phases with the endogenous circadian rhythm due to exposure to artificial LAN, changes in activity levels, alertness, cognitive function, and meal schedules caused to the schedules of night shift work⁹⁷. The misalignment between external environmental cues and the internal circadian rhythm may thus result in sleep disturbances, altered secretion hormones like melatonin and cortisol, and disruption in appetite regulation¹³⁵.

7.1. Prevalence of night shift work

Worldwide, it is estimated that 1 out of 5 workers are engaged in night shift work ¹⁴⁵. The Sixth European Working Conditions Survey in 2015 reported that 19% of employees are engaged in night work, while 21% are in shift work ¹⁴⁶. In the USA, the National Health Interview Survey (NHIS 2015) revealed that approximately 26% of workers were involved in shift work, whether in the evening, at night, or on rotating shifts ¹⁴⁷.

In Europe, the prevalence of night shift work had been relatively stable until 2015 (19% in 2005 and 19% in 2015) ¹⁴⁶. However, European Working Conditions Survey 2021 showed a relatively large proportion of employees engaged in night shift work (38%, Fig 9), indicating a sharp rise in the prevalence of night shift work encompassing a wide range of jobs worked at least 2 hours between 10 pm and 5 am ¹⁴⁸. The same survey reported a night shift work prevalence of 35% (25% among females, 43% among males) in France in 2021, with 13% reporting frequent night shift work ¹⁴⁸. In France, from 1982 to 2015, alongside the growth in the total workforce, night shift workers (usual and occasional) steadily increased from 15.8% in 1982 to 16.4% in 2015 ¹⁴². However, the past decade has witnessed a significant rise in the proportion of night shift workers of all types. This increase may be attributed to the overall expansion of the workforce in general and the demand for 24-hour services in more modernized societies. The industries requiring 24-hour services and involving non-standard work schedules are accommodation and food, art and entertainment, retail, transport and warehousing, and health and social assistance ^{149,150}. The occupations that more frequently require night-time hours are often the ones with low wages, such as security guards, waiters/waitresses, nurses, home-health aides, janitors, construction workers, and laborers, suggesting that low socioeconomic status and lesser control over the work condition are often linked with night shift work ^{143,151}.

Figure 9: Employees working at night (at least 2 hours between 22h and 5h) in Europe (all and by gender) and France, shown as proportion of response ¹⁴⁸.



7.2. Definition and assessment of night shift work

Broadly, night shift work can refer to employment that occurs during the usual sleeping hours of the general population, typically involving work performed between 11 PM and 7 AM. This type of work disrupts the natural circadian rhythms due to alterations in the environmental light-dark schedule. Night shift work can include fixed-location work, such as in hospitals, factories, and call centers, and trans-meridian travel, such as aircrew duties. There are various types of night shift work, including:

- Fixed/Permanent Night Shifts: Employees work night shifts on a regular, ongoing basis with fixed schedules or hours.
- Alternating/Rotating Shifts: Employees alternate between day and night shifts on a regular schedule, with or without a fixed direction of rotation.
- Irregular Shifts: Employees work night shifts on an unpredictable or ad-hoc basis.

Different definitions are employed for varying purposes. For regulatory context, the International Labour Organization defines night shift work as any work performed during a period of not less than seven consecutive hours, including the interval from midnight to 5 am ¹⁵². In France, work schedules are subject to precise legal regulations defined by the Labor

Code. Night work is legally defined as any professional activity between 9 pm and 6 am (art. L3122-29 of the Labor Code) ¹⁵³. A night worker is identified as any employee whose regular work schedule includes at least three hours of work during this period at least twice a week or an employee who performs a minimum number of night hours over a reference period, as established by agreement or convention. In the absence of such an agreement, the minimum number of night hours required is 270 hours over 12 months (art. L3122-31 and L3122-8) ¹⁵³. These definitions provide essential aspects such as work timing, frequency, and duration.

IARC's monograph suggested a more restrictive definition of night shift work as "having worked at least 3 hours between midnight and 5 am" as a required minimum exposure to estimate the sleep perturbation created by the night shift and the shift in circadian rhythm ¹³⁸. Besides this definition of night shift work, the monograph highlighted multiple other characteristics that need to be considered to assess night shift work exposure and capture its effect on different aspects of chrono disruption ¹³⁸. Table 1 outlines critical domains and variables for assessing night shift work in epidemiological studies. These domains include working time, night work duration, intensity, cumulative exposure, and characteristics of shift schedules, among others, each capturing unique aspects of how night shift work impacts circadian rhythms, which is crucial for understanding the potential health risks, particularly breast cancer. The major domains are:

1. Shift system: This domain includes features of night shift work such as start time of shift, number of hours per day, rotating or permanent, speed and direction of a rotating system, and regular or irregular night shift work.
2. Duration and cumulative exposure: This domain include the total years on a particular night shift schedule and cumulative exposure to the shift system over the working life.
3. Intensity: This domain includes features like time off between successive work days on the shift schedule and consecutive days of shift.
4. Individual disposition: This domain includes individual characteristics such as chronotype.

These domains provide a comprehensive measurement allowing a detailed assessment of the dose-response relationship and the cumulative burden of night shift work on cancer risk, including but not limited to breast cancer.

Table 1: Domains and variables for assessment of night shift work exposure and its impact on circadian rhythm ¹³⁸.

Domain	Variable	Circadian Impact
Night work	At least 3 hours of work between midnight and 5 am	Required to estimate phase shift and sleep perturbation
Working time	Work hours/week	
Duration	Years employed in night shift work	Duration of night shift work
Intensity	Number of night shifts per month/year	Recovery time off between work periods
Cumulative exposure	Duration times intensity over the work history	Dose (burden) of night shift work
Permanent night shift (not rotating)	Number of consecutive days of night work, followed by number of days off	Permanent night work is less disruptive only if the phase shift is maintained also on days off
Rotating type	Continuous (365 days/year) or discontinuous (interruption on weekends)	Different rotating shift schedules have a different impact on phase shift and adjustment
Direction of rotation	Forward (morning /afternoon /evening /night) backward (afternoon /evening /morning /night)	Forward-rotating shift schedules are less disruptive than backward ones
Rate of rotation	Daily change, 2-3-4 day change, weekly, fortnightly change	Rate of rotating shift schedules (fewer nights in a row) may have different impacts on circadian disruption
Morning shift	Number of consecutive days of early morning shift (before 06:00)	The earlier the morning shift starts, the more disruptive it is
Start and end times of shifts	Defines displacement from solar day and duration of the working hours	May be relevant for phase shift, sleep deficit, and fatigue
Rest periods after the shift	Number of rest days after night shifts	The shorter the rest period between shifts, the shorter the sleep and recovery
Jetlag	Number of time zones crossed: eastward versus westward	Only needed in cohort studies of frequent trans-meridian travelers (e.g., air crews); jetlag studies should also include shift work questions
Sleep	Sleep duration in relation to type of shift; naps; sleep quality; sleepiness; sleeping problems (circadian disruption); possibility to sleep on duty (night shifts)	Sleep/wake cycle and timing of sleep are important in phase shift and resetting, but they may also act as independent risk factors
Light at night	During sleep period, during night shift, during leisure time	Both timing and intensity are important in circadian phase shift
Characteristics of the individual	Diurnal type/chronotype (morning person, evening person, neutral)	It influences adjustment and tolerance to night and morning shifts differently

7.3. Literature review on night shift work and breast cancer

Night shift work and its effect on the risk of breast cancer have been frequently studied over the years, and many studies have reported an increased risk of breast cancer due to night shift work exposure. The studies that have reported a positive association between breast cancer risk and night shift work and its features are commonly case-control studies¹⁵⁴⁻¹⁵⁹, and less frequently cohort studies^{96,160}. A summary of selected case-control and cohort studies that assessed the association between night shift work exposure and breast cancer risk are provided in Annex 1 and 2, respectively.

In the existing literature, exposure to night shift work has been assessed using different measurements⁹⁵. While most studies have reported the risk estimates for the categories of ever or never having worked night shifts, duration, and intensity of night shift work, the criteria used to define night shift work vary. The definitions used in these studies ranged from broader criteria, such as working between 5 pm and 9 am for a year¹⁵⁵, or less restrictive, such as working any or at least hour between 11 pm to 5 am¹⁵⁹ or more restrictive such as having worked between 12 pm and 6 am¹⁶¹. Some studies based their definition of night shift work solely on occupations such as nurses working at the hospital¹⁶² working as flight attendants¹⁵⁶ or simply counted nights in a month regardless of start or end time¹⁶⁰.

In an attempt to harmonize the definition of night shift work exposure, a comprehensive pooled analysis was conducted using five population-based case-control studies in Australia, Canada, France, Germany, and Spain¹⁶³. This pooled analysis is considered superior because of its methodological rigor. It re-coded the night shift work exposure using the definition of "having worked for at least 3 hours between midnight and 5 am". The findings from this study indicated an overall increased risk of breast cancer among night shift workers, with an OR of 1.12 (95% CI: 1.00-1.25). The study also noted that the risk increased with longer durations of night shift work (≥ 10 years) and higher intensity (≥ 3 nights/week). The risk was found to be higher in pre-menopausal women (OR 1.26, 95% CI: 1.05-1.51) compared to post-menopausal women, as well as for estrogen receptor-positive (ER+) and estrogen receptor-positive/human epidermal growth factor receptor 2-positive (ER+/HER2+) breast cancer subtypes.

The epidemiological studies that have used cohort study design, except for a few, have reported null findings (Annex 1, 2). A recent mega-study combined three prospective cohort

studies in the UK: the Million Women Study, EPIC-Oxford, and UK Biobank, and assessed the association between night shift work and breast cancer risk while using the original definition of these three studies ¹⁶⁴. The study defined night shift work as having worked at night for any time between midnight and 6 am for at least 3 nights per month for the Million Women Study, 1 night per month on a regular basis for a year in EPIC-Oxford, and included any substantial night work for the UK Biobank. The findings across all three cohorts consistently showed no significant association between night shift work and breast cancer risk. Specifically, the Million Women Study reported an OR of 1.00 (95% CI: 0.92-1.08), the EPIC-Oxford cohort found an OR of 1.00 (95% CI: 0.81-1.22), and the UK Biobank reported an OR of 0.78 (95% CI: 0.61 - 1.00). This study also reported further on a meta-analysis of 10 cohort studies, including the aforementioned 3 prospective cohorts, and reported a pooled relative risk of 0.99, 95% CI: 0.95-1.03 ¹⁶⁴. These findings contradict those from the pooled analyses of case-control studies. However, this study has been criticized by the scientific community for the potential exposure misclassification, recall biases, and short follow-up time, as well as the inter-study heterogeneity in the meta-analysis ^{150,165,166}.

Overall, there is a contradiction between the results presented by cohort and case-control studies, underscoring the differences in the exposure assessment methods. Even though cohort studies are generally considered superior to case-control study design, there has also been a recent shift in preference toward case-control study design as being more appropriate to assess complex exposures such as night shift work itself ¹⁶⁷.

Heterogeneity across the study population is also speculated to contribute to the inconsistent results ¹⁴⁰. Many studies that exhibited positive results are usually conducted in a specific population, such as nurses ^{154,160,162}, flight attendants ¹⁵⁶ and military personnel ¹⁶⁸. Some studies involving the general population or women across several occupations showed a positive association for a longer exposure duration of 30 years or more ^{157,159,169}.

The results from the existing epidemiological studies are inconsistent despite many studies reporting a positive association. Some meta-analyses ^{95,170} but not all ¹⁶⁴, indicate a moderately augmented risk of breast cancer among women as a result of exposure to night shift work. A meta-analysis including 26 studies showed a positive pooled estimate of 1.13 (95% CI: 1.03-1.34) for having worked at night shift jobs for <10 years, whereas for having worked ≥10 years at night shift jobs, the pooled estimate was statistically nonsignificant despite being positive

(RR: 1.08, 95% CI: 0.99-1.17)⁹⁵. The pooled estimates are apparently smaller for cohort studies (RR for <10 years: 1.02, 95% CI: 0.97–1.06 and RR for ≥10 years: 1.01, 95% CI 0.95–1.07) compared to those for case-control studies (<10 years: 1.25, 95 % CI: 1.8–1.44, ≥10 years: 1.22, 95% CI: 1.02–1.46)⁹⁵. A more recent meta-analysis including 33 studies has reported a positive pooled estimate of 1.20 (95% CI: 1.10-1.31) for both cohort and case-control study designs combined¹⁷⁰. This metaanalysis also reported a higher risk for >10 years of night shift work (RR: 1.12, 95% CI: 1.01-1.23) and even higher risk if the duration of night shift work is longer than 30 years (RR: 1.18, 95% CI:1.02-1.36)¹⁷⁰. A quality assessment of seven metaanalyses emphasized substantial methodological variations between the epidemiological studies conducted among varying populations and with varying methods to define and assess night shift work exposure¹⁴⁰.

Following the initial IARC evaluation in 2007, several pieces of scientific evidence have been produced, and numerous new informative epidemiologic studies were evaluated in the 2019 IARC monograph on night-shift work. Despite the overall positive associations found, night-shift work continued to be classified as a probable human carcinogen concerning breast cancer (Group 2A) based on "limited" evidence of carcinogenicity in human epidemiologic studies. This limitation was primarily due to the variability in exposure assessment, heterogeneity in the study population, incomplete measurement of the exposure, and inconsistent findings arising from them across studies with different designs.

8. LIGHT AT NIGHT

In natural settings, night-time light is mainly emitted from the moon, other planets, and the stars. The electrical light emitted from several anthropogenic sources alters this natural lighting, thus leading to “light pollution”¹⁷¹. Light pollution may occur in several forms, such as sky glow, light trespass, glare, or over-illumination. Sky glow occurs when water droplets or air particles scatter light into the atmosphere; light trespass is when light is incident to unintended surfaces such as streetlights emitting lights into the buildings; lights that shine horizontally cause glare; while over-illumination occurs when light is used beyond the required activity in offices, industries, or commercial buildings¹⁷². A significant amount of LAN results from the extensive use of street lights, billboards, automobiles, shops, and industrial lighting, which not only interfere with the natural lighting in the outdoor environment but also penetrate the indoor environment^{129,173}. Only approximately 40% of light emitted by street lights is useful, out of which 20% of light incident on urban surfaces are reflected (Fig 10), and a small proportion is used for human vision purposes, meaning that a considerable proportion of light emitted in the environment contributes to light pollution^{171,172}. In addition, indoor settings are full of electronic devices such as televisions, mobile phones, tablets, computers, etc., emitting significant light into the sleep environment.

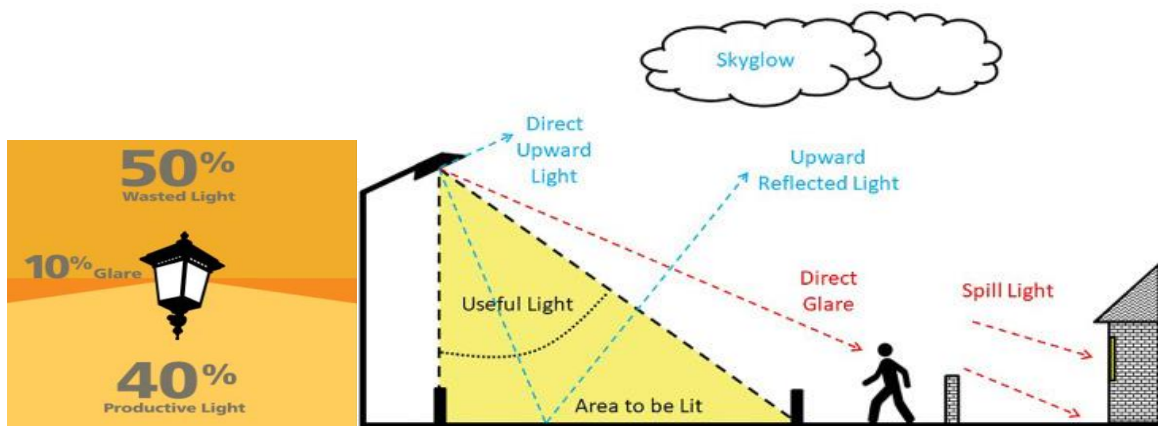


Figure 10: Left: Proportion of light distributed in different directions from a street light¹⁷³, Right: Dispersion of light and components of light pollution¹⁷⁴.

8.1. Spectral composition of visual light

The light emitted by electric lamps and electronic devices has a specific spectral distribution of wavelengths from 400-700 nm (Fig 11). Depending on the sources of electric light, the spectral distribution can vary; for example, LED lights primarily emit light around a wavelength

of 450 nm, fluorescent lights are of a range of 440-610 nm, and mercury vapor lights emission is of 540-580 nm ¹⁷⁵. The light with higher wavelengths shows warmer colors like yellow and orange, while the shorter ones appear more white or bluish, perceived as brighter than the warmer-colored light ¹⁷¹. The light emission of a shorter wavelength, ~450–480 nm, also known as “blue light,” is often considered hazardous to human health ¹⁷⁶. Effects on human health vary depending on the spectral components of artificial light. Exposure to blue light with a shorter wavelength for 6 hours or longer has been found to increase alertness, cognitive functions, and brain activities at night ¹⁷⁷. In addition, blue light is also linked to higher degrees of circadian disruptions ¹²⁷ and is becoming a focus of scientific studies concerning its implications on breast cancer risk.

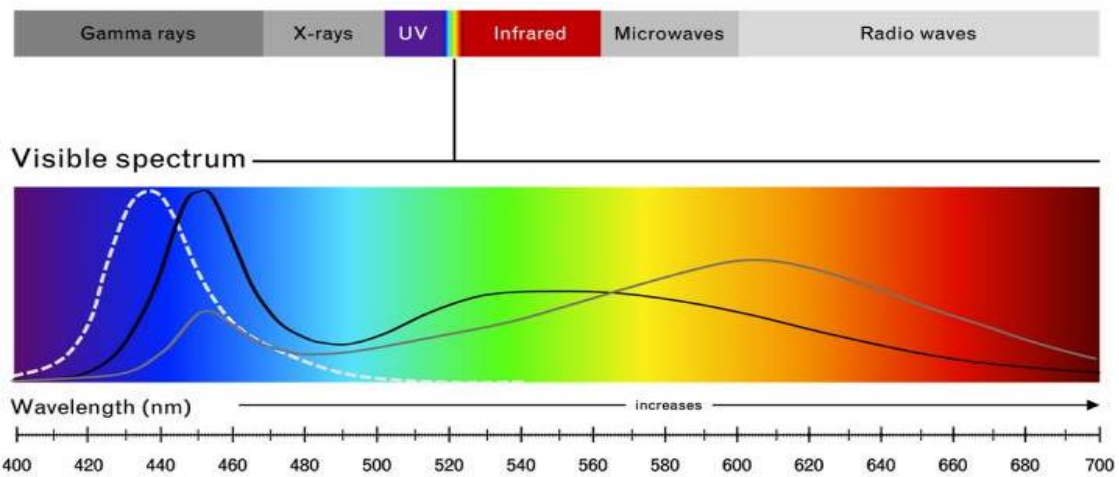


Figure 11: Visible light and the wavelengths of its spectral component within the electromagnetic spectrum ¹⁷⁶.

8.2. Measurement and quantification of light pollution

Light pollution and exposure to LAN are challenging to measure as the exposure varies depending on the source, distance, and perceived brightness ¹⁷¹. Exposure to LAN can be measured on different levels using various tools, which can be spaceborne, airborne, or ground-based ¹⁷⁴. A summary of the most commonly used tools for the measurement and quantification of light pollution can be found in Table 2.

Table 2: Different tools commonly used to measure light pollution ^{174,178}.

Type of tools	Temporal measurement	Geographical coverage	Spatial resolution	Spectral range	Unit of measurement	Temporal availability	Cost
Satellite-based measurements							
DMSP/OLS Satellite	Monthly and Annual composites of upward light	Available for all countries	30 arcsec grid size (~1 km at the equator)	500-900 nm	W/cm ² /sr	1992–2013	Free
VIIRS/DNB Satellite	Daily, monthly, and annual composites of upward light	Available for all countries	30 arcsec grid size (~1 km at the equator)	500-900 nm	W/cm ² /sr	2012-	Free
Astronaut's photo from ISS	Remote red-green-blue (RGB) imaging of upward light	Major cities for almost all countries	5-200m	RGB	W/cm ² /sr Cd/m ²	2003-	Free
Luojia-1 satellite	Bi-monthly remote imaging of upwards light	China and selected areas	130m	460-980 nm	W/m ² /sr/μm	2018–2019	Free
Airborne measurements							
Aircraft / Drone/ Balloon	Varying measurements of upward light	Regional or on-demand	Depends on cameras used	Depends on cameras used	Depends on cameras used	On-demand	On-demand depends on instrument and coverage

Type of tools	Temporal measurement	Geographical coverage	Spatial resolution	Spectral range	Unit of measurement	Temporal availability	Cost
Ground-based measurements							
Luminance meters	One-dimensional local light	Local	Depends on instrument used	380-780 nm	lx, cd/m ²	On-demand	From €120
Wearable devices	One-dimensional local light	Local	Depends on instrument used	350-780 nm	lx	On-demand	NA
Digital cameras	RGB imaging of upward or local light	Regional/ Local	Depends on instrument used	RGB	Cd/m ² Lv, Lx, mag/arcsec ²	On-demand	NA
US National Park Service all-sky	RGB imaging of upward light	Regional	Depends on the instrument used	400-650 nm	V mag/arcsec ²	On-demand	NA
Imaging smartphone apps	Upward or local light	Regional/ Local	Depends on app	Depends on app	Depends on app	On-demand	Free or low-cost
Spectro meters	Spectral imaging of upward or local light	Regional/ Local	Depends on instrument used	350-780 nm	µm pixels I, V mag/arcsec ²	On-demand	NA
Hyperspectral cameras	Hyperspectral imaging of upward or local light	Regional/ Local	Very high ~ 0.72 nm	RGB	Pixel	On-demand	On-demand depends on instrument and coverage

DMSP-OLS: Defense Metrological Satellite Program/Operational Linescan System, ISS: International Space Station, NA: Information not available in the literature RGB: Red Green Blue, VIIRS/DNB: Visible Infrared Imaging Radiometer Suite/Day Night Band

8.2.1. Satellite-based measurements

The satellite-based tools measure the light at global or regional levels based on data collected by satellites at cloudless night at various time points, which is then provided as a composite value ¹⁷⁹. Primary satellite-based sources are the Defense Metrological Satellite Program/Operational Linescan System (DMSP/OLS), the Day Night Band of the Suomi National Polar-Orbiting Partnership Visible Infrared Imaging Radiometer Suite (VIIRS/DNB), and the images taken by astronauts at International Space Station (ISS) ¹⁷⁴. Satellite-based measurements are the most commonly used method to assess exposure to outdoor LAN. However, the data from each source differs in terms of temporal availability, spatial resolution, spectrum measurement, and spatial coverage, and sometimes, calibration and data saturation issues are based on their resolution ^{174,178}. Most studies on light at night and breast cancer risk have used images from either DMSP ¹⁸⁰ even though they have limitations of low resolution and low variability of data in urban areas ¹⁸¹. The images from ISS provide the highest resolution images that can differentiate between the Red-green-blue range and are used in a Spanish multi-case-control study only ¹⁸². However, the temporal availability for ISS images is more recent than others, and the geographical availability is limited to major cities in most countries.

8.2.2. Airborne measurement

The air-borne tools measure the upward light through instruments mounted on crewed or uncrewed aircraft. These tools are not commonly preferred for epidemiological studies on breast cancer risk because of high costs, aviation regulations, and spectral limitations ¹⁷⁴.

8.2.3. Ground-based measurements

The ground-based tools measure the light with a relatively smaller spatial coverage. Pertaining to their ease of access and use, these tools are very commonly used in research; however, they are accompanied by limitations of spectral sensitivity, human errors, and device limitations ¹⁷⁴. Besides, some self-reported measures of light pollution in indoor and outdoor settings are also commonly used in studies despite their imprecision and other methodological limitations ¹⁷⁴. Studies exploring exposure to LAN and breast cancer have used satellite-based measurements for outdoor exposure assessment and self-reported measures for indoor exposure assessment ¹⁸⁰.

8.3. Development of electric light and light pollution

The invention of incandescent light bulbs by Thomas Edison in 1879 gave rise to the modern era of electric light ¹⁷². Having existed for approximately 150 years, the electric light has become an indispensable part of daily life ¹¹⁹. The electric light evolved from the incandescent bulbs in the 1800s to fluorescent lights, metal halide, sodium/ mercury vapor lights, compact fluorescent lights, and light-emitting-diodes (LED) in the present ¹⁸³. This widespread development and adoption of electric light have made life and activities possible 'round-the-clock,' creating a 24/7 society where artificial light is also abundant at nighttime ¹⁷¹. At present, more than ever, daily lives have become dependent on electric light. Indeed, almost all mundane activities, such as the use of electronic devices and machinery, recreation, occupations, transportation, and many more, depend on artificial light. As a result of the inevitable urban development and transformation into urban lifestyles, exposure to LAN has become quite inescapable. Individuals are surrounded by numerous sources of artificial light in indoor and outdoor settings, thus making "LAN" commonplace in the modern world ^{179,184}.

8.4. Trends in light pollution

The recent atlas of night sky brightness shows that more than 80% of the world and more than 99% of the U.S. and European populations live under light-polluted night skies ¹⁸⁴. Consequently, many countries in the world, predominantly European and American countries, have experienced a widespread "loss of night" ¹⁷³ and substantially modified "light-dark cycles." Light pollution is growing as one of the newest forms of environmental pollution worldwide. The countries with the brightest LAN are Kuwait, Qatar, United Arab Emirates, Saudi Arabia, South Korea, and Israel, where most of the population live under a very bright night sky ¹⁷⁹. Countries like Chad, Central African Republic, and Madagascar still have ample natural night light. The countries with the most polluted night sky in Europe are Belgium, Netherlands, Italy, and the United Kingdom (Fig 12). From 2012 to 2016, artificial light intensity has grown annually by more than 2% globally ¹⁷⁹. This growth in lighting was speculated to be associated with, among other factors, economic growth and the transition to efficient light-emitting-diode (LED) lighting ¹⁷⁹. At present, natural light cycles are only found within 13.2% of the total environmental spaces, distributed across only 0.2% of the land surfaces on Earth ¹⁸⁵.

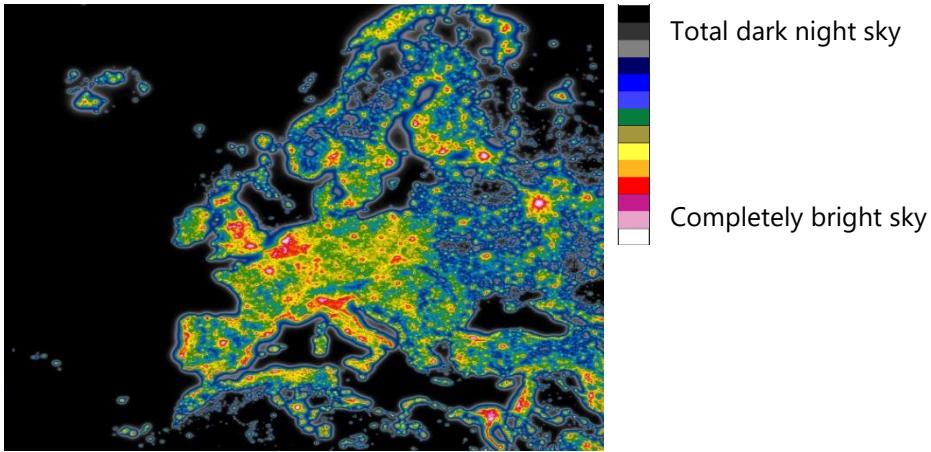


Figure 12: Night sky brightness across Europe ¹⁸⁴.

Among the G20 countries, France is one of the most light-polluted countries, with more than 60% of the area under the light-polluted night sky ¹⁷⁹. From the year 1991 to 2013, the night light in France shows an increasing trend (Fig 13) with a sharp increase between 2009 and 2012, which could be suspected to be the result of growing urbanization and the installation of more streetlights and bill-boards, etc., along with the transition to the LED light ¹⁸⁶. However, a decreasing trend was observed between 2012 and 2019 ¹⁸⁷, with major cities still under light-polluted night sky as of 2020 (Fig 14).

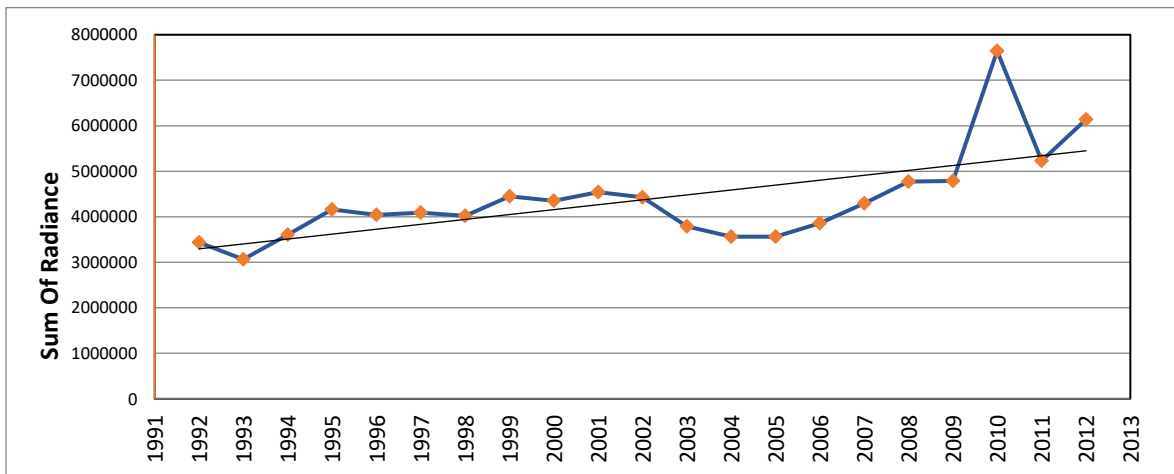


Figure 13: Evolution of light at night (as total sum of radiance) in France between 1991 and 2013 ¹⁸⁸.

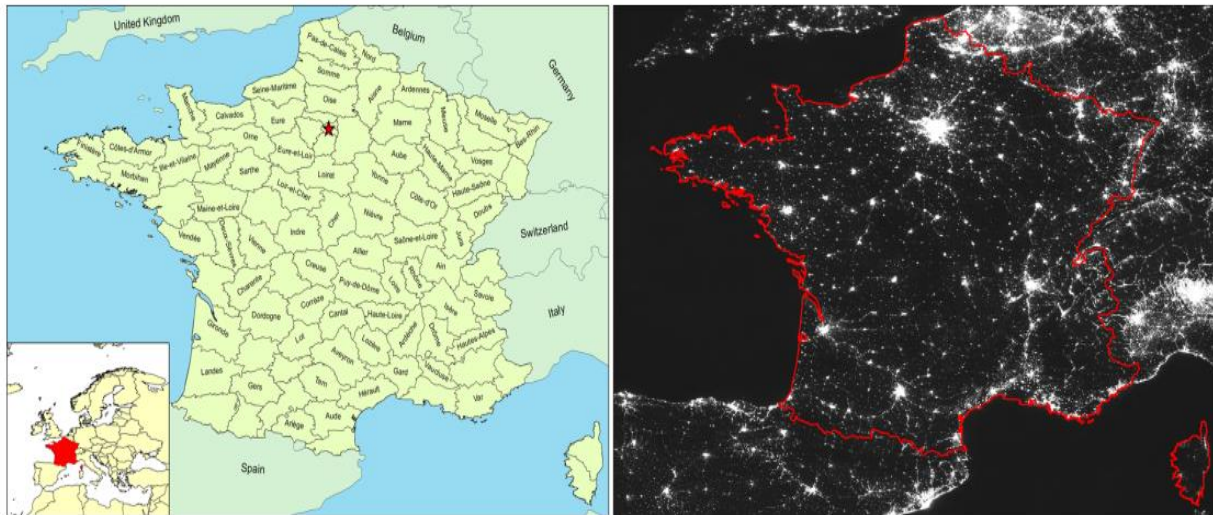


Figure 14: Left: Demographic map of France, Right: LAN in France for December 2019, observed using VIIRS-DNB indicated with white colors for major cities and black for less populated geographical regions such as rural area ¹⁸⁷.

8.5. Light at night and urbanization

Nightlights indicate human activities, and their intensity can reflect variations in urbanization while correlating with socioeconomic status ¹⁷⁸. Higher intensity of night light results from higher degrees of socio-economic activities, such as those associated with industries, airports, hospitals, hotels, and supermarkets ¹⁸⁹. Urban lifestyles and occupations necessitate late-night shifts and prolonged use of electronic devices, which contribute to higher exposure to LAN ¹¹⁹. Light pollution also entails a complex interaction between the light emitted by urban sources and the constituents of the atmosphere ¹⁹⁰. Higher concentrations of air pollutants in the urban environment increase the skyglow, thus intensifying the loss of natural night light in urban areas ¹⁹¹. Thus, the distribution of LAN and the shift in natural light-dark phases could be expected to be widespread in urban areas rather than rural areas. In rural areas, fewer street lights, fewer economic activities, lower air pollution, and lots of vegetation also result in lesser intensity of LAN ¹⁹². Satellite observations have shown that between 2002 and 2012, global growth in light emission occurred globally in areas where artificial LAN was already present, such as urban areas, peri-urban areas, or isolated small cities ¹⁸⁵. The variation in LAN exposures in urban or rural areas is crucial regarding breast cancer risk since the incidence of breast cancer is seen to be higher in high-income urban areas ¹¹² and living in urban areas also signifies higher exposure to other potential risk factors for breast cancer such as air and noise pollution. In addition to the rural-urban differences in LAN exposure, temporal and

seasonal variations can be expected due to changes in activities during weekdays vs weekends or changes in night light in summer vs winter ¹⁷⁸.

8.6. Impacts of LAN on environment and human health

Even though artificial light has undoubtedly benefited human lives, adverse environmental and health effects are inevitable. Disruption of the natural light cycles has been shown to have several impacts on the environment and human health ¹⁸⁵. Since the biological systems are organized by daily and seasonal light cycles, a long-term alteration of natural light-dark cycles due to artificial LAN strongly disrupts biological processes at the individual, species, community, and, potentially, whole ecosystem scales ¹⁷³. Nocturnal artificial light affects the organisms' nightlife patterns by affecting their migration, nutrition, reproduction, and collective action ¹⁹³. Vegetation and its ecosystems are also affected by changes in light-dark cycles, altering their growth, resource allocation, and pollinators' and herbivores' behavior ¹⁹⁴. Besides, it has also been linked with other environmental functions, such as greenhouse gas emissions through electric energy consumption and altering the nocturnal dynamic of chemical pollutants in several cities ¹⁷³.

Many studies have linked LAN and alterations of several physiological functions in human beings. Light is often associated with poor sleep and sleep-related outcomes, possibly disrupting sleep ¹¹⁹. In addition, LAN is also suspected to be associated with mood disorders, depression, and poorer overall mental health ^{119,195}. Experimental and observational studies have also linked physiological changes caused by LAN and metabolic syndromes, diabetes, obesity along with cardiac diseases and the risk of breast cancer ^{124,125,128,129}. As light is the primary cue for circadian rhythm, the suspected mechanisms behind these adverse effects of LAN on human health are i) circadian rhythm disruption, ii) inhibition of melatonin and its oncostatic properties, and iii) responses to the varying wavelengths of the visible electromagnetic spectrum ¹⁹⁶.

8.7. Literature review on outdoor LAN and breast cancer risk

Breast cancer, as a hormone-dependent cancer, is sensitive to alterations in endocrine function caused by circadian disruption-related alteration of melatonin. The study of light at night and its impact on circadian disruption and breast cancer risk is relatively recent. There is a growing scientific interest in the association between LAN exposure and breast cancer risk. Countries with high HDI, where the majority of the population living under light-polluted night sky, have observed a high incidence of breast cancer^{30,184}. Several ecological studies have reported a positive association between higher outdoor LAN and breast cancer risk^{112,197,198}. However, only a limited number of observational studies have assessed the exposure to outdoor LAN and its association with breast cancer risk. A summary of previously conducted studies on the association of outdoor LAN and breast cancer risk can be found in Annex 3.

Six cohort studies^{199–204} and six case-control studies^{182,205–209} have investigated breast cancer risk due to the exposure to outdoor LAN assessed using satellite images and/or questionnaires on sleeping habits. All six cohort studies and two case-control studies^{205,206} used DMSP satellite images for LAN assessment at the residential addresses of participants, while one case-control study used ISS images for this purpose¹⁸². Positive associations with breast cancer risk were found in several cohort studies^{200,202–204} and two case-control studies when comparing the highest levels of outdoor LAN to the lowest^{182,206}. However, other studies reported no association between breast cancer risk and outdoor LAN^{199,201,205,208–210}. These conflicting results may arise from inter-study variations in outdoor LAN assessment and statistical methods.

Studies utilizing satellite reported a heightened risk of breast cancer ranging from 3% to 47% among women exposed to the highest intensity of LAN compared to those exposed to the lowest^{182,200,202–204,206}. The MCC-Spain Study, the only study that used ISS images, demonstrated the highest risk estimate of 1.47 (95% CI: 1.00–2.17) using the Melatonin Suppression Index (MSI), a proxy for blue light exposure^{127,182}. However, this study showed no association between breast cancer risk and exposure to regular visual light (OR: 0.81, 95% CI: 0.54–1.20). These findings from the MCC-Spain Study provide evidence that blue light is the most disruptive of circadian rhythm and the most inhibitive of melatonin secretion, thus associating with a higher risk of breast cancer.

Additionally, studies using satellite images are heterogeneous regarding the exposure metrics and the duration of exposure assessment. Some studies used DMSP images to assess outdoor LAN exposure for periods ranging from 9 to 16 years of period^{182,199,200,203,206}, considering the residential history and corresponding changes in exposure. In contrast, other studies used only a single-time assessment of the outdoor LAN^{202,204}. While using LAN assessment over time, it is crucial to account for potential changes in the exposure levels due to residential re-location, as LAN can vary with urbanization levels. Furthermore, heterogeneity among these studies also arises from the differences in the source of satellite images, their temporality, and spatial and spectral resolutions.

Some studies used interviews and questionnaires to assess sleep habits over 10-15 years prior to the study date to evaluate exposure to outdoor LAN^{207,209,210}. These include indicators such as the use of curtains, blinds, or shutters and the presence of night light to be used as proxies for exposure to outdoor LAN in indoor settings. Two studies using these measures found no significant association between exposure and risk of breast cancer^{208,209}. Notably, one study used "residing near strong LAN sources" as a proxy for outdoor LAN exposure and found a positive association with breast cancer risk (OR: 1.52, 95% CI: 1.10-2.12)²¹¹. However, studies using interviews and questionnaires do not objectively measure outdoor LAN exposure; they are subject to exposure misclassification due to recall bias. In contrast, LAN assessment using satellite images offers greater precision, a lower risk of exposure misclassification, and a possibility of retrospective exposure measurement.

Another issue in previously conducted studies is the limitation in acknowledging the concurrent indoor LAN exposure and other crucial environmental exposure alongside other established risk factors of breast cancer. Breast cancer, being a complex disease with many established risk factors, necessitates adequate adjustment for these factors, particularly in the context of exposure to LAN, which usually does not occur in isolation. Thus, it is also crucial to consider urban-environmental exposures. Only Garcia-Saenz et al., 2018 adjusted for indoor LAN exposure, while only Clarke, 2021 and Sweeney et al., 2022 accounted for air pollution, noise pollution, and residential greenness. Furthermore, only a few studies considered potential confounding due to night shift work^{199,203,205}.

Furthermore, the available literature does not provide conclusive results on the effect modification by factors such as menopausal status, ER status, and other lifestyle and environmental factors. Some studies suggested a higher risk for post-menopausal women^{202,204}, while others reported a higher risk for pre-menopausal women^{200,203}. Some studies provided no evidence at all for the effect modification by menopausal status^{182,199,205} or ER status²⁰⁵ or elevated BMI^{199,200}, or urbanicity and air pollution¹⁹⁹. Studies that assessed the exposure to LAN based on sleep habits^{209,212}, the presence of outdoor light²¹⁰, and self-reported LAN exposure²¹³, showed no evidence of effect modification by menopausal status or by estrogen receptor status.

The inconsistent results and heterogeneity among the studies make the literature on outdoor LAN and breast cancer risk inconclusive, highlighting gaps in the literature concerning the LAN assessment methods and potential confounding due to other possible risk factors. A recent meta-analysis¹⁸⁰ including eight studies on exposure to outdoor LAN, provided a pooled risk estimate of 1.11 (95% CI: 1.07-1.16) for the highest level of exposure compared to the lowest. This meta-analysis also reported a higher pooled estimated for pre-menopausal women: 1.22 (95% CI: 1.08-1.39) from 4 studies, compared to post-menopausal women: 1.07 (95% CI: 1.00-1.32) pooled from 5 studies. However, due to the small number of studies included and their heterogeneity, there is a need for cautious interpretation of the results.

9. THESIS OBJECTIVES

The incidence of breast cancer is increasing and is expected to rise in the coming years, making it a growing public health concern. While the roles of lifestyle and genetic factors in breast cancer etiology are well documented, environmental and occupational factors remain insufficiently explored. With the modernization and rapid growth of the global workforce, women today are increasingly exposed to environmental risks such as artificial light at night and night shift work. These factors contribute to circadian disruption, which has been implicated as a potential risk factor for hormone-dependent cancers, including breast cancer.

Circadian disruption, characterized by alterations in the body's internal clock, is challenging to measure directly in large-scale epidemiological studies, as it often requires the assessment of biomarkers like melatonin levels, which are resource-intensive and time-consuming to obtain. However, exposure to light at night and night shift work are considered practical proxies for circadian disruption and can be more feasibly assessed in large populations.

Despite a growing body of literature investigating the relationship between night shift work, light at night, and breast cancer risk, conclusive links have not yet been established due to various limitations and gaps in the available research. These limitations include inconsistencies in exposure assessment methods, inadequate control for confounding variables, and variability in study designs. This thesis, therefore, aims to provide a comprehensive study on the effects of circadian disruption, specifically through exposure to light at night and night shift work, and their associations with breast cancer risk in the French population. By addressing the gaps in existing research, this study seeks to contribute valuable insights into the environmental and occupational determinants of breast cancer, which could have public health implications.

9.1. General objectives

To study the role of exposure to artificial light at night or working at night in breast cancer risk in a French population.

9.2. Specific objectives

1. To study the role of environmental exposure to artificial light at night in breast cancer risk in the context of a case-control study, the CECILE Study
2. To study the role of environmental exposure to artificial light at night in breast cancer risk in the context of a large prospective study, the E3N-Generations Cohort
3. To study the role of night shift work in breast cancer risk in the context of a general-population based cohort, the CONSTANCES Cohort

10. ORGANIZATION OF THE THESIS

This thesis conforms to the regulations and guidelines of Université Paris-Saclay. The first chapter provided an introduction to breast cancer and exposure to light at night and night shift work. The second chapter will focus on the light at night and breast cancer risk based on the CECILE study, the third chapter will also focus on the light at night and breast cancer risk based on the E3N-Generations cohort, and the fourth will focus on night shift work and breast cancer risk based on CONSTANCES cohort. Each chapter will entail details on material, methods, and statistical analysis strategies applied to fulfill the thesis objectives, along with the main results, sensitivity analyses, and a discussion. The fifth chapter will provide a general discussion of the main findings from the three studies/analyses, the validity of the thesis, public health implications, an overall conclusion, and future perspectives. Supplementary material can be found in the appendices.

**CHAPTER 2: OUTDOOR LIGHT AT NIGHT AND BREAST CANCER RISK IN
THE CECILE STUDY**

1. STUDY OBJECTIVES

This chapter addresses the first objective of this thesis, which examines the association between exposure to outdoor light at night and breast cancer risk within the context of a population-based case-control study in France. Subsequent sections will detail the materials and methods used to conduct the analyses, present the main findings, and discuss the results.

2. MATERIALS AND METHODS

2.1. Study design and population

The CECILE study, which stands for *Cancers du sein: Etude épidémiologique en Côte d'Or et en Ille-et-Vilaine sur l'Environnement*, is a population-based case-control study conducted between 2005 and 2007 in two French departments, *Côte d'Or* and *Ille-et-Vilaine* situated in Eastern and Western part of France, respectively (Fig 15). The primary objectives of the CECILE study were to investigate the role of environmental and occupational risk factors in the etiology of breast cancer.

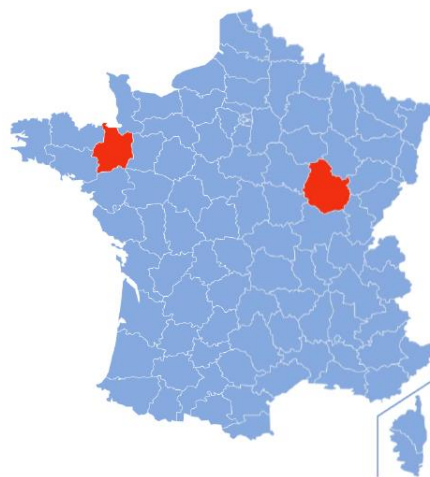


Figure 15: Departments of Côte d'Or and Ille-et-Vilaine within the map of France ²¹⁴.

2.2. Recruitment of cases and controls

Females aged 25-75 years, residents of *Côte d'Or* and *Ille-et-Vilaine*, and diagnosed with histologically confirmed in-situ or invasive breast cancer between April 2005 and March 2007 were eligible for inclusion as cases. In *Ille-et-Vilaine*, cases were recruited from the main cancer hospital in Rennes (*Centre Eugène Marquis*) and smaller public and private hospitals (*Centre*

Hospitalier Saint-Grégoire, Hôpital de Saint-Malo) in an attempt to recruit all women diagnosed with breast cancer during the study period in the department. In *Côte-d'Or*, cases were almost exclusively recruited from the main cancer hospital in Dijon (*Centre Georges-François Leclerc*), which treated most breast cancer patients in the department. Of the 1,556 eligible cases identified, 163 declined to participate, 151 could not be contacted, 7 died before the interview, and 2 had incomplete occupational history, resulting in 1232 (79.3%) cases for inclusion in the study.

Eligible controls were women from the general population of the two departments with no history of breast cancer, who were invited to participate in the study by a polling institute using randomly selected phone numbers. Controls were frequency-matched to the cases by 10-year age group and department, according to the principles of incidence density sampling. In addition to frequency-matching cases and controls, the distribution of the control group by socioeconomic (SES) category was kept similar to that of the general population of women in the departments to minimize potential selection bias that could result from differential participation rates between SES groups. To achieve this, we applied quotas during the selection procedure in seven SES categories (farmers, self-employed workers, managers, technicians, employees, manual workers, and inactive women) ²¹⁵. Of the 1,731 eligible controls identified, 260 refused to participate, 154 could not be contacted, and 2 had incomplete work histories, resulting in 1,315 (76%) controls that could be included in the study.

The local ethical committee approved the study protocol, and all subjects signed informed consent before enrolling in the study.

2.3. Data collection

Between 2005 and 2008, cases and controls were interviewed face-to-face by trained interviewers using standardized questionnaires. The questionnaire was designed to capture a wide range of information, including sociodemographic data, medical history, family history of cancer, anthropometric measurements, reproductive history, lifestyle factors, and residential and occupational history. The interviews lasted 60- 90 minutes and took place either at the participants' homes or at the hospital in some instances. During these sessions, blood and saliva samples were also collected from participants. The reference date was defined as the date of diagnosis for cases and the date of informed consent for controls.

Pathology reports were retrieved from medical records to verify the tumor's stage, grade, histology, and hormone receptor status. Tumors with more than 10% positive hormonal receptor cells were characterized as receptor-positive.

2.3.1. Sociodemographic characteristics

Information on date of birth, education level, occupation, marital status, ancestry, and a complete residential history were collected during the face-to-face interviews.

2.3.2. Medical, reproductive, and lifestyle-related characteristics

Information on personal medical history and family history of cancer was collected during the interviews, along with information on hormonal and reproductive factors such as age at menarche and menopause, oral contraceptive use, menopausal hormonal therapy (MHT) use, history of gynecological diseases and surgeries (hysterectomy, oophorectomy), outcomes of each pregnancy, duration of breastfeeding and infertility treatment.

Information on lifestyle-related factors such as alcohol consumption, smoking, recreational physical activities, dietary habits, and occupational history, along with height (at age 20 and a year before the interview) and weight (at age 20, a year before the interview and at different ages) were also collected during the interview. Information on dietary habits was collected through a self-administered questionnaire.

2.3.3. Geocoding of residential history

The residential history of all participants was collected for 10 years before the date of reference. The residential history included addresses and duration of stay in each address. All the residential addresses were geocoded using the ArcGIS software and BDadresse in ArcGIS.

2.4. Exposure assessment

Exposure to outdoor LAN was assessed by using the satellite images of the Operational Linescan System (OLS) available in the Defense Meteorological Satellite Program (DMSP) of the National Oceanic and Atmospheric US Administration (NOAA). The DMSP/OLS was initially used in the early 1970s for cloud imaging, but it was later discovered that nighttime photographs were capable of detecting visible light emissions sources like city lights, auroras, gas flares, and fires ²¹⁶. The digital archive of these images was created from 1992 onwards,

making the image accessible for various scientific applications. The DMSP/OLS captures images globally twice per day across 3000 km swaths ²¹⁷. During the last two decades, nine OLS satellites have been launched to capture nighttime images ²¹⁶. These satellites have a unique capability of detecting low-light imaging data at night and detecting moonlight clouds, lights from cities, towns, industrial sites, gas flares, and ephemeral events such as fires and lightning-illuminated clouds. The satellite images provide composite values on cloud-free illuminance after excluding light from the sun, moon, aurora, and seasonal fires ²¹⁸. The images are available from 1990 onwards but are not radiance calibrated; thus, the data from these images are saturated in urban centers.

In this study, we used the Radiance Calibrated Nighttime Lights Products, available from 1996 onwards. The radiance-calibrated images have a higher dynamic range, better spatial resolution, and better data quality compared to the uncalibrated images ²¹⁹. The high-dynamic range radiance calibrated images have a spatial resolution of a 30-arc second grid (~ 650 x 650 m) ²¹⁹. The illuminance was measured in nanowatts per square centimeter per steradian (nW/cm²/sr).

Table 3: Availability of radiance-calibrated DMSP images, their temporal range, and application in the CECILE study.

Year	Temporal range	Study period
1996	March 16, 1996–February 12, 1997	1995-1997
1999	January 19 –December 11, 1999	1998-1999
2000	January 3 – December 29, 2000	2000-2001
2003	December 30, 2002–November 27, 2003	2002-2003
2004	January 18 –December 16, 2004	2004
2006	November 28, 2005–December 24, 2006	2005-2007

Outdoor exposure to LAN was assessed at each address occupied by women during the 10 years before the reference date (i.e., 1995 to 2007). Table 3 shows the years where the radiance-calibrated images were available, their corresponding temporal coverage, and the years in the study for which the satellite data was used. For the years when satellite images were unavailable, the data from the closest year was used. The satellite data provided an annual composite of the luminosity value at a given location. These images were then projected in geographic information system software (GIS) – ArcGisPro 3.0 and cross-

referenced with the geocoded locations of each address to estimate annual exposure for all women at each residential address. Then, the cumulative exposure to outdoor LAN over the 10 years was calculated as an average of annual exposures weighted on the length of stay at each address. This process allowed us to consider the changes in the levels of exposure to LAN at different residential locations when the women changed their residential addresses.

In the primary analysis, two metrics were used to assess exposure to outdoor LAN: in a continuous form and categorical form using the tertiles based only on the exposure distribution among controls.

3. ANALYTICAL STRATEGY

A series of statistical methods were applied to assess the association between exposure to outdoor LAN and breast cancer risk. Initially, descriptive statistics were used to characterize the demographics and key attributes of the study population. The analysis of the distribution of outdoor LAN exposure among the study population followed this. Subsequently, regression models were applied to obtain the risk estimates for this association. These models were rigorously evaluated to ensure the robustness and reliability of the findings.

3.1. Participants included in the analysis

Out of 2,548 (1,233 cases and 1,315 controls) women, 55 women (30 cases and 25 controls) had missing geocoded addresses and missing values for LAN, while 26 had outlying values for LAN and were further excluded, leaving 2,467 women for the main analysis.

3.2. Choice of covariates

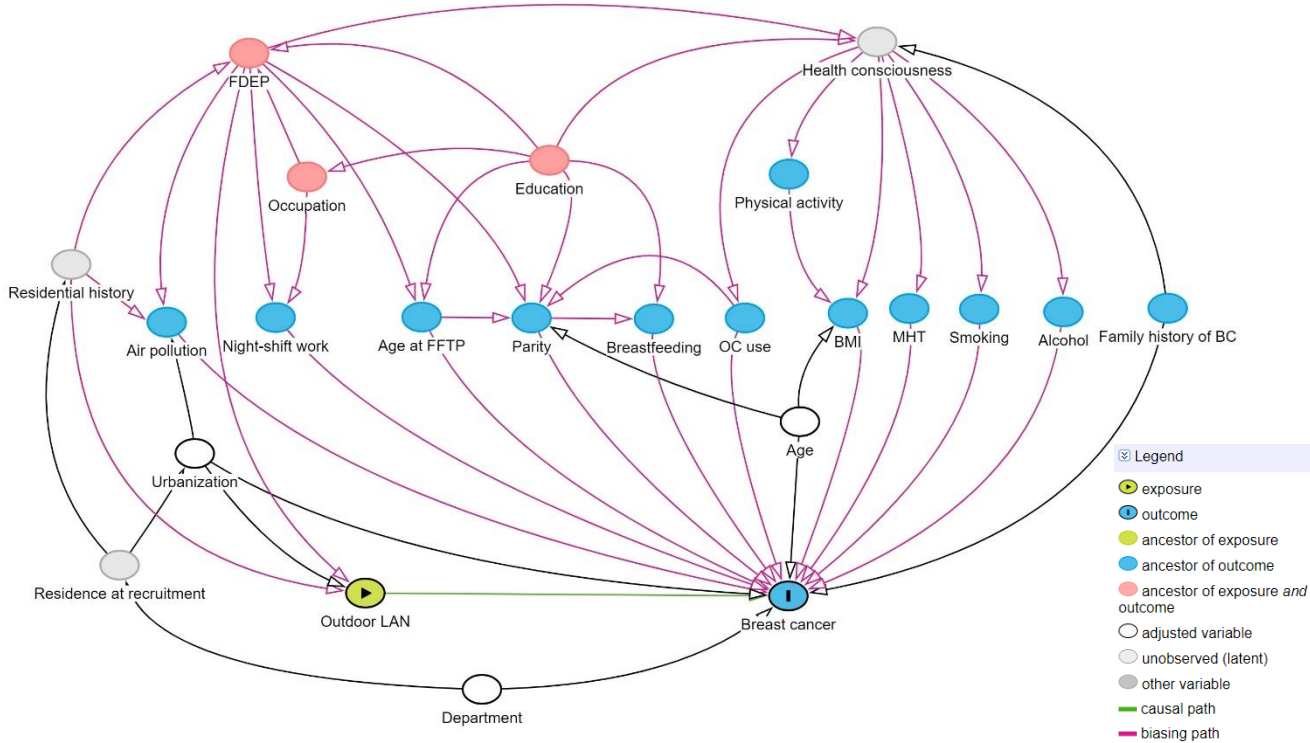
The variables to be considered as potential confounders and included in the main analyses were selected using the Directed Acyclic Graph (DAG) approach^{199,220}. Potential covariates considered in this study are shown in Fig 16 which included age at reference, department of residence at reference, age at first full-term pregnancy, parity, menopausal status, oral contraceptive use, MHT use, family history of breast cancer in first-degree relatives, alcohol consumption, smoking, body mass index (BMI), recreational physical activity, night shift work, educational level (proxy for SES), occupation, urbanization of the residential area at reference, and exposure to air pollution. The matching factors of age and department of residence were forced into the DAG. The urbanization level was also forced in the DAG to account for a

different participation rate between cases and controls by levels of urbanization. The causal links between the covariates, outdoor LAN, and breast cancer were drawn based on a priori information from available literature. DAG was drawn using the DAGitty software ²²¹.

The following minimal adjustment set of potential confounders was identified and used in the main analyses. This set covered a wide range of breast cancer risk factors that were adequately measured in our study and would reduce the residual confounding.

"Age, Age at FFTP, Air pollution, Alcohol, BMI, Department, Education, Family history of BC, MHT, Night-shift work, OC use, Parity, Smoking, Urbanization"

Figure 16: DAG for the association between outdoor exposure to LAN and breast cancer risk in the CECILE Study.



BC: Breast cancer, BMI: Body-mass Index, FDEP: French Deprivation Index, FFTP: First full-term pregnancy, LAN: Light at Night, MHT: Menopausal hormonal therapy, OC: Oral contraceptives

3.2.1. Definition of variables included in the analysis

Age

Age at reference date was calculated using the date of birth for all participants, the date of diagnosis for cases, and the date of interview for controls. Age was adjusted in all models as a continuous variable.

Department of residence

Study participants were selected from either *Côte d'Or* or *Ille-et-Vilaine* and are the department of residence at the reference. date

Urbanization level

The urbanization level of the area of residence was determined using participants' residential addresses at the time of recruitment. The urbanization was classified based on the urban unit where their home address was. An urban unit is defined as a commune or group of communes where the buildings are continuously built up (with no more than 200 meters between two buildings) and house at least 2,000 inhabitants. According to the 2007 French population census and the 2010 geographical layout of French territory, the National Institute of Statistics and Economic Studies ²²² categorized urban units into four types: main city, suburb, small town, and rural area. Urban units that included multiple communes or multi-commune agglomerations were classified as central cities or sub-urban areas based on the communes' population size and spatial structure. Those situated in a single commune were designated as isolated cities. Communes that did not conform to the urban unit criteria were identified as rural areas. The analysis categorized urbanization into central cities, sub-urban areas, isolated cities, or rural areas.

Education level

Information on the highest education levels attained was collected through face-to-face interviews at recruitment and was categorized into four levels in the analysis: primary school or lower, basic secondary school, secondary school, and university education. Education was used as a proxy for socio-economic status (SES).

Family history of breast cancer

Information on family cancer history among first-degree relatives was used as a binary variable (yes, no) in the models. First-degree relatives include parents, siblings, and children ²²³.

Parity

Parity is defined as the number of full-term pregnancies and was determined using pregnancy information collected during the interview. Parity was used as a categorical variable in the models with 4 categories: nulliparous, 1, 2, and ≥ 3 full-term pregnancies.

Age at first full-term pregnancy

The age at first full-term pregnancy among parous women was categorized into 3 categories: <22, 22-24, 25-27, and >27 years.

Oral contraceptives

Oral contraceptive use at recruitment was categorized as a binary variable: ever, never.

Menopausal status and menopausal hormonal therapy use

Menopausal status was determined using a combination of hormonal and reproductive factors. Women were categorized as pre-menopausal if they were still menstruating on the reference date, had menstruated within the last 12 months, were on oral contraceptives that halted menstruation, were not menstruating due to breastfeeding, or had not had a total bilateral oophorectomy. Conversely, women were considered post-menopausal if their last menstrual period occurred more than 12 months before the reference date, they had undergone a total bilateral oophorectomy, or they were using menopausal hormonal therapy. For women who had undergone a hysterectomy or whose last menstrual period was unknown, menopausal status was determined based on age: those under 50 were classified as pre-menopausal, while those 50 and older were classified as post-menopausal.

Menopausal hormonal therapy (MHT) included estrogen-only or estrogen-progesterone treatments among post-menopausal women. In the models, a combined variable of menopausal status and MHT was used with three modalities: pre-menopausal women, post-menopausal women with MHT use, and post-menopausal without MHT use.

Body mass index

BMI one year before the reference date was calculated from height and weight information gathered during the in-person interview. The World Health Organization's (WHO) BMI classification was used to categorize the BMI variable: <18.5, 18.5-24.9, 25-29.9, and ≥ 30 kg/m².

Physical activity

The intensity of physical activity during leisure time was assessed using the units of metabolic equivalents (MET), which indicates the energy expenditure for each type of activity. As per the Compendium of Physical Activities, values of MET were assigned for each type of physical activity²²⁴. For each activity, the activity-specific MET values were multiplied by the time spent

in the activity (i.e., number of hours per year, number of years) to calculate units of MET-hours per week per year. Values of MET for all recreational activities were summed to produce a lifetime recreational physical activity variable, which was categorized into four levels: <1, 1-2.9, 3-7.9, and >8 MET-hr/week/year.

Tobacco consumption

Tobacco smoking was used as a categorical variable with 3 categories: non-smokers, former smokers, and current smokers.

Alcohol consumption

The lifetime alcohol consumption variable was calculated as the average number of glasses consumed per week during adult life (since age 20). A glass of alcohol corresponds to one unit of alcohol, measured as 10g²²⁵. This variable was divided into four categories: never, 0-3, 4-7, and ≥ 7 glasses per week.

Night shift work

Night shift work was defined as having worked for at least 3 hours between midnight and 5 a.m. in at least one job for a minimum of 6 months during the entire career. In the analyses, it was used as a binary (ever, never) variable.

Air pollution

Exposure to three air pollutants, nitrogen dioxide (NO₂) and particulate matter (PM_{2.5} and PM₁₀), was assessed at the women's residential address over 10 years before the reference date. The concentrations of each air pollutant at each address were estimated using nationwide Gazel-Air models, which provided annual estimates at a 2 km resolution scale across France⁹⁹. In the models, the average of the annual concentrations ($\mu\text{g}/\text{m}^3$) of NO₂, PM_{2.5}, and PM₁₀ during the 10 years prior to the reference date were used in continuous forms.

Tumor subtypes

The data collected on estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) status were utilized to classify breast cancer into 3 subtypes: i) hormone-receptor positive (i.e., estrogen receptor-positive or progesterone receptor positive and human epidermal growth factor receptor 2 negative (ER+ or PR+ and HER2-), equivalent to the luminal A molecular subtype); ii) HER2+ regardless of ER and PR

status, equivalent to the luminal B and HER2- enriched molecular subtypes; and iii) triple-negative tumors (ER-, PR- and HER2-).

3.3. Statistical methods

A descriptive comparison was made between cases and controls for their sociodemographic, reproductive, hormonal, lifestyle-related characteristics and other environmental exposures using chi-square tests for categorical variables and Wilcoxon signed-rank tests for continuous variables at a statistical significance level of $p = 0.05$. Multivariable unconditional logistic regression models were applied to calculate the odds ratios (ORs) and the corresponding 95% confidence intervals (CIs) for the main analyses of the association between exposure to outdoor LAN and breast cancer risk.

For the exposure in continuous form, ORs and 95% CI were calculated per one interquartile range (IQR = 159.9 nW/cm²/sr) increase in the exposure, based on exposure distribution among controls only. To assess the association for varying levels of exposure, tertiles of exposure were created, also based on the exposure distribution among the controls only. In the models, the first tertile (T1) was considered the reference group, indicating the lowest level of exposure; the ORs and 95% CI were calculated for 2nd and 3rd tertiles of outdoor LAN (T2 and T3).

Model 1 was adjusted for the matching variables (age at recruitment and department of residence at recruitment) and the urbanization level of the place of residence at recruitment.

Model 2 was further adjusted for other potential confounders identified in the minimal adjustment set, including education, age at first full-term pregnancy, parity, oral contraceptive use, menopausal status and MHT use, history of breast cancer among 1st-degree relatives, BMI, alcohol consumption, tobacco smoking, and night shift work.

Model 3 was further adjusted on air pollution using exposure to NO₂, PM_{2.5}, and PM₁₀ alternatively.

Exposure to outdoor LAN and air pollution can occur concurrently, particularly in areas with higher levels of urbanization. Consequently, a correlation between exposure to outdoor LAN and air pollution could be anticipated. The Pearson correlation coefficient was used to assess this correlation between exposure to outdoor LAN and air pollutants. Additionally, possible

collinearity between these exposures while using them in the same regression model was assessed using the variance inflation factor (VIF) in Model 3. The VIF indicated collinearity if greater than 5²²⁶.

Further analyses explored the modification of the association between outdoor LAN exposure and breast cancer by potential effect modifiers, including department, menopausal status, night shift work, urbanization, education, and BMI. Effect modification by the department was assessed to determine variations due to differential enrollment of cases and controls across departments. Considering that the risk of breast cancer may vary by menopausal status and may be influenced by hormonal, reproductive, and environmental factors, it was hypothesized that outdoor exposure to LAN could be associated with breast cancer differently according to menopausal status. As a proxy for socio-economic status, education was a potential effect modifier because higher socio-economic status, often associated with living in urban areas, may alter outdoor LAN exposure. Additionally, night shift work, which typically involves high indoor exposure to LAN and other circadian disruptors, was also assessed for effect modification to explore its differential effect on the association of outdoor light at night and breast cancer risk. Previous findings within the study population indicated that BMI levels could influence breast cancer risk; therefore, our analyses aimed to determine if the association also varies by BMI levels.

Further, the associations of outdoor LAN exposure with different tumor subtypes were also assessed.

3.3.1. Sensitivity analysis

Considering the relevance of outdoor LAN exposure in urban areas often accompanied by other urban exposures such as air pollution, we conducted a sensitivity analysis only including women who lived in non-rural areas, allowing a detailed analysis of the possible confounding effect of exposures to air pollutants in urban settings.

We also estimated the minimum detectable ORs for this study. Estimations of the minimum detectable OR in the CECILE study can be found in Annex 4.

All statistical analyses were conducted using SAS software version 9.4 (Cary, North Carolina).

4. RESULTS

4.1. Descriptive characteristics

A comparative description of sociodemographic, personal, lifestyle-related, reproductive hormonal, and environmental characteristics of the cases and control status is shown in Table 4.

4.1.1. Sociodemographic characteristics

The study comprised 1,185 (48%) cases and 1282 (52%) controls. The distribution of cases and controls by age and department were similar. In our data, cases lived more often than controls in urban areas like central cities (33% vs. 27 %) and sub-urban areas (17% vs 14%), while more controls than cases lived in rural areas (36% vs 27%). The distribution of educational attainment among cases and controls differed, with more cases (27%) having a university degree or higher than controls (23%).

4.1.2. Lifestyle-related, reproductive, and hormonal characteristics

The cases were more likely to have an earlier average age at menarche than controls and to be nulliparous or with 2 or fewer children than controls. More cases (25%) had their 1st full-term pregnancy at 28 years of age or later than controls (16%). Menopausal status did not differ significantly among cases and controls, but more post-menopausal cases were likely to be current users of menopausal hormonal therapies (20% vs 15 %). Pre-menopausal cases were, on average, thinner than controls, whereas BMI did not differ significantly among post-menopausal women. Cases more frequently had a family history of breast cancer than controls (17% vs 11%). No difference was observed between the two groups in oral contraceptive use, alcohol consumption, smoking status, or night shift work.

4.1.3. Environmental exposure

Among the cases in this study, the mean annual exposure to NO₂, PM_{2.5}, and PM₁₀ was higher than that among the controls.

Odds ratios and their corresponding 95% confidence intervals for the association of these variables with the breast cancer risk independent of the exposure in this study can be found in Annex 5.

Table 4: Descriptive characteristics of participants in the CECILE study (n=2467), 1990-2007.

	Cases (n=1185)	Controls (n=1282)	p -values[†]
Department, n (%)			
<i>Côte d'Or</i>	369 (31.1)	442 (34.5)	0.08
<i>Ille-et-Vilaine</i>	816 (68.9)	840 (65.5)	
Age at reference			
Mean ± SD	55.4 ± 10.6	55.4 ± 11.0	0.21
10 - years age groups			
25-35 yrs	39 (3.3)	42 (3.3)	0.76
35-45 yrs	171 (14.4)	175 (13.6)	
45-55 yrs	362 (30.6)	388 (30.3)	
55-65 yrs	349 (29.5)	363 (28.3)	
65-75 yrs	264 (22.8)	314 (24.5)	
Urbanization, n (%)			
Main cities	393 (33.1)	352 (27.5)	<0.001
Suburbs	211 (17.8)	186 (14.5)	
Isolated cities	256 (21.6)	280 (21.8)	
Rural areas	325 (27.4)	462 (36.1)	
Education level, n (%)			
No school/ Primary	271 (22.9)	298 (23.2)	0.04
Basic Secondary	427 (36.0)	507 (39.6)	
Secondary	162 (13.7)	187 (14.6)	
University degree	325 (27.4)	290 (22.6)	
Age at menarche			
Mean ± SD	12.93 ± 1.6	13.11 ± 1.7	<0.01
Parity, n (%)			
Nulliparous	126 (10.6)	83 (6.5)	<0.001
1	182 (15.4)	165 (12.9)	
2	472 (39.8)	458 (35.7)	
≥3	405 (34.2)	576 (44.9)	
Age at 1st full-term pregnancy ^a, n (%)			
<21 yrs	262 (24.7)	347 (28.9)	<0.001
22-24 yrs	306 (28.9)	381 (31.8)	
25-27 yrs	232 (21.9)	279 (23.3)	
≥28 yrs	259 (24.6)	192 (16.0)	
Menopausal status, n (%)			
Pre-menopausal	468 (39.5)	480 (37.4)	0.30
Post-menopausal	717 (60.5)	802 (62.6)	
BMI (kg/m²) among Pre-menopausal			
<18.5	25 (5.3)	13 (2.7)	0.01
18.5-24.9	324 (69.4)	300 (62.6)	
25-30	83 (17.8)	114 (23.8)	
≥30	35 (7.5)	52 (10.9)	
BMI (kg/m²) among Post-menopausal			
<18.5	16 (2.2)	21 (2.6)	0.89
18.5-24.9	357 (49.9)	406 (50.7)	
25-30	221 (30.9)	235 (29.3)	
≥30	121 (16.9)	139 (17.4)	

	Cases (n=1185)	Controls (n=1282)	p -values[†]
Menopausal hormonal therapy^b, n (%)			
Never	355 (49.5)	388 (48.4)	<0.01
Current	146 (20.4)	121 (15.1)	
Former	216 (30.1)	293 (36.5)	
Oral contraceptives use, n (%)			
Never	648 (56.7)	738 (57.6)	0.33
Former users	140 (11.8)	137 (10.7)	
Current users	397 (33.5)	407 (31.7)	
Breast cancer among 1st degree relatives, n (%)			
Yes	204 (17.2)	139 (10.8)	<0.001
No	981 (82.8)	1143 (89.2)	
Alcohol consumption, n (%)			
0-3 glasses per week	923 (77.9)	1065 (83.1)	0.35
4-7 glasses per week	151 (12.7)	183 (14.3)	
>7 glasses per week	111 (9.4)	132 (10.3)	
Smoking status, n (%)			
Never smokers	728 (61.4)	786 (61.4)	0.62
Former smokers	253 (21.4)	289 (22.6)	
Current smokers	204 (17.2)	205 (16.0)	
Night shift work^c, n (%)			
Never	1073 (90.5)	1171 (91.4)	0.54
Ever	110 (9.5)	110 (8.6)	
Air pollution (mean annual exposure during the 10 years before the reference date)			
Nitrogen-dioxide (NO₂ µg/m³)			
Mean ± SD	17.1 ± 6.7	16.2 ± 6.7	<0.001
Particulate matter 2.5 (PM_{2.5} µg/m³)			
Mean ± SD	13.7 ± 1.2	13.5 ± 1.3	<0.001
Particulate matter 10 (PM₁₀ µg/m³)			
Mean ± SD	21.7 ± 1.5	21.5 ± 1.6	0.12

a: parous women only, b: menopausal women only, c: night shift work defined as at least 3 hours between 12-5 a.m. at least in one job during the whole career, BMI: Body-mass Index; LAN: Artificial Light at night, † p-values derived from χ^2 for categorical variables and Wilcoxon signed-rank test for continuous variables.

4.2. Distribution of exposure to outdoor LAN

Throughout 1995-2005/7, the annual exposure to LAN was found to have an overall increasing trend among controls. Urban areas like central cities and sub-urban areas also observed an increase in annual exposure to outdoor LAN over 10 years. Line charts and tables showing mean annual exposures to outdoor LAN among controls and by urbanization from 1995 to 2007 can be found in Annex 6. Table 5 shows the LAN exposure distribution among cases and controls, and corresponding boxplots can be found in Annex 7. Exposure to outdoor LAN was higher among the controls who resided in the *Cote-d'Or department compared to the Ille-et-Vilaine* department. The exposure was higher in the main cities (median among controls, IQR:

232.4, 72.2-358.0 nW/cm²/sr and suburbs (median among controls, IQR: 110.7, 63.3-203.6 nW/cm²/sr). Levels of exposure were relatively higher among women with university degrees. There was no significant difference in the exposure level by night shift work. LAN exposure increased with increasing exposure to NO₂ and PM_{2.5}. The exposures to all three air pollutants (NO₂, PM_{2.5}, and PM₁₀) had a significant positive correlation with LAN exposure in our data. The correlation matrix for LAN exposure and air pollutants can be found in Annex 8.

Table 5: Distribution of outdoor LAN exposure (nW/cm²/sr) by strata of selected covariates in the CECILE study, 1990-2007.

	Cases (n=1185)		Controls (n=1282)	
	Mean ± SD	Median (Q1-Q3)	Mean ± SD	Median (Q1-Q3)
Department				
Cote-d'Or	160 ± 153.2	100.3 (24.0-287.7)	137.4 ± 150.5	55.5 (16.53-253.2)
Ille-et-Vilaine	115.5 ± 116.5	68.5 (19.2-176.0)	96.5 ± 111.0	43.4 (13.22-150.5)
Urbanization				
Main cities	230.3 ± 138.8	256.0 (85.1-350.6)	222.6 ± 146.1	232.4 (72.2-358.0)
Sub-urban areas	150.4 ± 106.4	121.4 (66.8-207.3)	141.7 ± 102.9	110.7 (63.3-203.6)
Isolated cities	76.4 ± 70.8	44.1 (24.2-117.3)	77.5 ± 78.9	40.5 (23.06-117.1)
Rural areas	35.2 ± 62.9	11.5 (7.7-25.8)	32.6 ± 63.5	10.7 (7.51-21.4)
Education				
No school/ Primary	98.6 ± 117.3	40.7 (13.4-153.5)	75.1 ± 102.7	22.9 (10.1-108.2)
Basic Secondary	113.6 ± 119.4	62.5 (18.4-179.7)	97.8 ± 122.9	37.1 (12.4-130.5)
Secondary	136.9 ± 136.8	78.1 (19.1-225.2)	128.0 ± 131.3	76.2 (22.7-213.6)
University degree	171.9 ± 140.9	128.5 (49.1-301.6)	158.0 ± 139.9	114.0 (29.4-271.9)
Night shift work				
Never	129.6 ± 131.1	72.7 (20.5-217.4)	108.8 ± 126.5	43.7 (13.6-169.3)
Ever	125.1 ± 124.3	75.5 (21.3-183.8)	129.8 ± 136.7	71.1 (19.5-232.4)
NO₂ in tertiles (µg/m³)				
T1 (5.3-11.7)	30.6 ± 35.7	15.5 (8.0-37.6)	24.2 ± 30.0	12.3 (7.8-28.2)
T2 (11.7-19.2)	85.1 ± 79.5	54.4 (24.8-130.0)	78.1 ± 77.9	47.1 (21.5-109.9)
T3 (19.2-41.9)	254.0 ± 121.3	267.2 (156.9-351.5)	255.1 ± 125.5	264.5 (148.5-362.3)
PM_{2.5} in tertiles (µg/m³)				
T1 (8.7-13.2)	54.6 ± 58.9	26.7 (11.0-86.6)	48.3 ± 57.0	22.6 (9.5-71.0)
T2 (13.2-14.3)	80.7 ± 102.3	37.7 (15.5-91.0)	67.3 ± 93.6	23.2 (11.4-76.6)
T3 (14.3-22.8)	239.3 ± 125.9	239.3 (130.0-348.3)	235.4 ± 134.8	232.4 (110.7-358.7)
PM₁₀ in tertiles (µg/m³)				
T1 (14.0-21.3)	153.8 ± 125.8	135.1 (32.0-257.2)	117.7 ± 114.3	81.4 (17.8-199.2)
T2 (21.3-21.9)	103.7 ± 114.3	61.4 (18.7-153.9)	86.5 ± 114.4	33.7 (13.4-89.9)
T3 (21.9-31.1)	129.7 ± 144.9	57.5 (15.6-198.8)	129.1 ± 148.6	58.4 (12.0-212.6)

4.3. Association between outdoor LAN and breast cancer risk

The odds ratios for breast cancer risk associated with outdoor LAN exposure are shown in Table 6. In Model 1, with basic adjustment for age, department, and urbanization, the odds ratios in T2 and T3 compared to T1 were 1.11 (95% CI: 0.86-1.41) and 1.25 (95% CI: 0.95-1.63), respectively. The OR for one interquartile range (IQR = 159.9 nW/cm²/sr) increase in LAN exposure was 1.09 (95% CI: 0.96-1.24). Further adjustment for reproductive and lifestyle-related factors in Model 2 reduced the ORs at T2 and T3 as well as for per IQR increase in LAN. Additional adjustment for NO₂ used as a marker of traffic-related air pollution resulted in further reduction of the ORs in T2 (1.05; 95% CI: 0.81-1.37) and T3 (1.10; 95% CI: 0.78-1.56) and for one IQR increase in LAN to 0.98 (95% CI: 0.81-1.52). Alternative adjustments for PM_{2.5} or PM₁₀ in Model 3 also reduced the ORs, although only a minor reduction was observed for PM₁₀.

Table 6: Odds ratios and 95% confidence interval for the association between outdoor LAN and breast cancer risk, adjusting for different covariates in the CECILE study, 1990-2007.

Outdoor LAN (nW/cm ² /sr)	Cases, n (%)	Controls, n (%)	Model 1	Model 2	Model 3		
			OR (95% CI)	OR (95% CI)	Model 2+ NO ₂ OR (95% CI)	Model 2+PM _{2.5} OR (95% CI)	Model 2+ PM ₁₀ OR (95% CI)
T1 (0-21.2)	306 (25.8)	426 (33.2)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
T2 (21.3-113.9)	404 (34.1)	429 (33.5)	1.11 (0.86-1.41)	1.07 (0.83-1.38)	1.05 (0.81-1.37)	1.06 (0.82-1.37)	1.06 (0.82-1.37)
T3 (114.0-477.1)	475 (40.1)	427 (33.3)	1.25 (0.95-1.63)	1.18 (0.89-1.56)	1.10 (0.78-1.56)	1.12 (0.83-1.52)	1.15 (0.86-1.52)
Per IQR increase	1185 (48.0)	1282 (52.0)	1.09 (0.96-1.24)	1.05 (0.92-1.20)	0.98 (0.81-1.17)	1.00 (0.86-1.17)	1.02 (0.89-1.18)

IQR=159.9 nW/cm²/sr based on the distribution of LAN among controls only, Model 1: Adjusted for age at reference, department, urbanization; Model 2: Model 1 + further adjusted on education, parity, age at first full-term pregnancy, menopausal status and menopausal hormonal therapy use, family history of breast cancer, oral contraceptive use, BMI, smoking, alcohol consumption, night-shift work Model 3: Model 2 + further adjustment on air pollution (NO₂ or PM_{2.5} or PM₁₀);

4.4. Effect modification of the association between outdoor LAN and breast cancer risk

In Table 7, we explored the effect modification by department, urbanization, education, menopausal status, night shift work, and BMI, also compared the effect before and after adjusting for exposure to NO₂ and found no effect modification. Further adjustment for air pollution (NO₂) decreased the ORs in most of the strata. The ORs tended to be slightly higher among women living in non-urban areas compared to rural areas and among post-menopausal women compared to pre-menopausal women.

Table 7: Odds ratios and 95% confidence interval for the effect modification of the association between outdoor LAN and breast cancer risk by variables of interest in the CECILE study, 1990-2007.

All women (n=2467)	Cases (n)	Controls (n)	OR (95%CI) ^a not adjusted for NO ₂	OR (95% CI) ^b adjusted for NO ₂	p for interaction
Departments					
Côte d'Or	369	442	1.03 (0.84-1.27)	0.90 (0.67-1.20)	0.55
Ille-et-Vilaine	816	840	1.08 (0.90-1.29)	1.05 (0.82-1.34)	
Urbanization					
Main cities	393	352	1.06 (0.89-1.26)	1.02 (0.77-1.37)	0.88
Suburbs	211	186	1.08 (0.82-1.17)	1.03 (0.68-1.56)	
Isolated cities	256	280	1.02 (0.69-1.49)	1.07 (0.68-1.68)	
Rural areas	325	462	0.96 (0.65-1.43)	0.76 (0.43-1.37)	
Education					
No school/ Primary	271	298	1.02 (0.72-1.44)	0.90 (0.57-1.42)	0.88
Basic Secondary	427	507	1.05 (0.84-1.31)	0.88 (0.65-1.20)	
Secondary	162	187	1.17 (0.81-1.67)	1.26 (0.75-2.13)	
University degree	325	290	1.04 (0.81-1.33)	1.03 (0.73-1.45)	
Menopausal status					
Pre-menopausal	486	480	0.90 (0.73-1.11)	0.85 (0.62-1.15)	0.12
Post-menopausal	717	802	1.15 (0.97-1.37)	1.07 (0.85-1.35)	
Night shift work					
Ever	110	110	0.84 (0.52-1.37)	0.87 (0.43-1.75)	0.14
Never	1073	1171	1.07 (0.93-1.23)	0.98 (0.81-1.19)	
Body-mass Index (kg/m²)					
<18.5	41	34	0.97 (0.41-2.31)	1.51 (0.35-6.41)	0.49
18.5-24.9	681	706	1.08 (0.91-1.28)	1.05 (0.82-1.35)	
≥25	460	540	0.98 (0.79-1.23)	0.84 (0.62-1.13)	

a: per one IQR increase in LAN (159.9 nW/cm²/sr) in the model adjusted for age at reference, department, urbanization, education, parity, age at first full-term pregnancy, menopausal status and menopausal hormonal therapy use, family history of breast cancer, oral contraceptive use, BMI, smoking and alcohol consumption (excluding the stratification factors for each stratification), b: further adjustment on air pollution (NO₂)

4.5. Association between outdoor LAN and breast cancer risk by hormone receptor status

We found no association between outdoor LAN and 'ER+/PR+ and HER2-' subtype or 'Triple negative' subtype in all women and neither by menopausal status (Table 8). The OR was higher for HER2-positive breast cancer (OR 1.56; 95% CI: 1.03-2.31), with an even higher OR for post-menopausal women (OR 2.15; 95% CI: 1.27-3.63) after adjusting for NO₂. This finding, however, should be approached with caution, given the small number of cases.

Table 8: Odds ratio and 95% confidence interval for the association between outdoor LAN and breast cancer by the hormone receptor status and menopausal status in the CECILE study, 1990-2007.

	Cases, n (%)	OR (95% CI) ^d not adjusted NO ₂	OR (95% CI) ^d adjusted NO ₂
All women (n= 2386) ^a			
ER+/PR+ and HER2-	873 (79.1)	1.01 (0.88-1.17)	0.92 (0.75-1.13)
HER2+	134 (12.1)	1.35 (1.02-1.79)	1.55 (1.03-2.31)
Triple-negative	97 (8.8)	1.04 (0.73-1.48)	0.81 (0.46-1.34)
Pre-menopausal women (n=916) ^b			
ER+/PR+ and HER2-	328 (75.2)	0.82 (0.64-1.04)	0.75 (0.53-1.06)
HER2+	64 (14.7)	0.95 (0.61-1.47)	0.89 (0.47-1.70)
Triple-negative	44 (10.1)	1.10 (0.66-1.85)	0.76 (0.34-1.67)
Post-menopausal women (n= 1470) ^c			
ER+/PR+ and HER2-	545 (81.6)	1.15 (0.95-1.39)	1.03 (0.80-1.33)
HER2+	70 (10.5)	1.80 (1.21-2.67)	2.15 (1.27-3.63)
Triple-negative	53 (7.9)	0.99 (0.59-1.67)	0.85 (0.43-1.67)

a: Full adjustment on age at reference, department, urbanization, education, parity, age at first full-term pregnancy, menopausal status and menopausal hormonal therapy use, oral contraceptives use, BMI, smoking, alcohol consumption, night-shift work b: models fully adjusted except for menopausal status and menopausal hormonal therapy use, c: models fully adjusted except for menopausal status, d: per one IQR increase in LAN (159.9 nW/cm²/sr)

4.6. Sensitivity analyses of the association between outdoor LAN and breast cancer risk restricted to urban residents only

Given the relevance of outdoor LAN exposure in urban areas, we conducted a sensitivity analysis restricting women who only lived in urban areas (n=1,679). This group included women living in central, sub-urban, and isolated cities. The tertiles of exposure and the IQR were recalculated based on the exposure distribution among controls in urban areas, considering the significant difference in the exposure distribution in rural and non-rural areas (Table 7). The sensitivity analyses showed that the women who lived in urban areas only, had higher ORs across all models than those among all women (Table 9). The ORs in the basic adjustment models were 1.35 (95% CI: 1.07-1.72) for T2 and 1.32 (95% CI: 0.98-1.63) for T3 with reference to T1. Small reductions in the odds ratios were observed, with further adjustment of reproductive and lifestyle-related factors in Model 2. On further adjustment on NO₂, there was a further reduction in the ORs in T1 (OR: 1.32, 95% CI: 1.01-1.72) and T2 (OR: 1.15, 95% CI: 1.80-1.63). Alternative adjustments on PM_{2.5} or PM₁₀ showed minimal to no change in the ORs. The ORs for per IQR increase (235.42 nW/cm²/sr) in the outdoor LAN exposure were also higher in this subgroup of women residing in non-rural areas (Model 3, adjusted for NO₂, OR: 1.01, 95% CI: 0.77-1.33) compared to all women (Table 9, Model 3 adjusted for NO₂, OR: 0.98, 95% CI: 0.81-1.17).

Table 9: Odds ratios and 95% confidence intervals for sensitivity analysis of the association between outdoor LAN and breast cancer risk among women living in urban areas only in the CECILE study, 1990-2007.

Outdoor LAN (nW/cm ² /sr)	Cases, n (%)	Controls, n (%)	Model 1 ^a	Model 2 ^b	Model 3 ^c		
			OR (95% CI)	OR (95% CI)	Model 2+ NO ₂ OR (95% CI)	Model 2+ PM _{2.5} OR (95% CI)	Model 2+ PM ₁₀ OR (95% CI)
T1 (0-55.6)	236 (27.4)	273 (33.3)	Reference	Reference	Reference	Reference	Reference
T2 (55.7-196.1)	318 (37.0)	272 (33.2)	1.35 (1.07-1.72)	1.38 (1.08-1.76)	1.32 (1.01-1.72)	1.36 (1.06-1.75)	1.38 (1.08-1.76)
T3 (196.2-477.1)	306 (35.6)	274 (33.5)	1.32 (1.04-1.69)	1.26 (0.98-1.63)	1.15 (0.80-1.63)	1.22 (0.91-1.64)	1.27 (0.98-1.64)
Per IQR increase	860	819	1.19 (0.99-1.42)	1.13 (0.94-1.36)	1.01 (0.77-1.33)	1.09 (0.87-1.37)	1.13 (0.93-1.37)

IQR=235.42 nW/cm²/sr based on distribution of LAN among controls only, Model 1: Adjusted for age at reference, department, urbanization; Model 2: Model 1 + further adjusted on education, parity, age at first full-term pregnancy, menopausal status and menopausal hormonal therapy use, family history of breast cancer, oral contraceptive use, BMI, smoking, alcohol consumption, night-shift work Model 3: Mode 2 + further adjustment on air pollution (NO₂ or PM_{2.5} or PM₁₀)

5. DISCUSSION

5.1. Summary of main findings

In this population-based case-control study, we found a suggestive association between exposure to outdoor LAN and breast cancer risk. A weak association was suggested in models unadjusted for air pollution, and the risk estimates decreased after adjustment for air pollution, an environmental exposure that correlates with outdoor LAN. Stratification by menopausal status, urbanization, education, night shift work, or BMI showed no apparent effect modification. At the same time, there was an indication of a potential association between outdoor LAN and breast cancer risk among women living in urban areas. Analyses by breast cancer subtype found a positive association with HER2+ tumor subtype based on a small number of cases.

5.2. Comparison with literature

Our findings corroborate with a previously conducted case-control²⁰⁵ and some cohort studies^{199,201} that have examined breast cancer risk as a function of environmental exposure to LAN assessed at the study subjects' home addresses, while contradicting with others^{182,200,202–204,206}. Five studies reported that women with the highest exposure to LAN had slightly augmented estimates of breast cancer risk compared to the group with the lowest exposure^{200,202–204,206}, while four other studies showed no increase in risk related to LAN exposure assessed in the full range of visible light^{182,199,201,205}. All of the studies measured exposure across the full spectrum of visible light from DMSP-OLS data, except the MCC-Spain Study (Garcia-Saenz et al., 2018), which assessed light intensity from nighttime photographs taken by astronauts aboard the International Space Station (ISS).

Two cohort studies reported no association with breast cancer risk after considering other environmental exposures correlated with LAN that may confound the association^{199,201}. The Nurses Cohort Study in Denmark reported a decreased hazard ratio after adjustment for air pollution and road traffic noise (Clarke, 2021); the US Sister Study cohort showed no association between LAN and breast cancer after adjustment for air pollution (NO₂, PM_{2.5}), noise pollution, and proximity to green spaces²⁰¹. Our study also found that adjusting for NO₂ exposure, a proxy for road-traffic-related air pollution associated with breast cancer risk¹⁰¹,

further reduced the ORs associated with outdoor LAN exposure. This finding is consistent with the two recent cohorts and suggests that air pollution needs to be considered to identify the independent effect of outdoor LAN on breast cancer risk. However, it is essential to exercise caution while considering factors that could be highly correlated with outdoor LAN, such as air and noise pollution. In our study, air pollution was individually correlated with outdoor LAN, which increased the risk of variation inflation and bias in our statistical models. To address this issue, we assessed multicollinearity using the VIF test and found no evidence of collinearity between air pollution and exposure to outdoor LAN in full models (results for multicollinearity tests are given in Annex 9). However, despite the absence of collinearity in the models, we could not successfully disentangle the independent effect of these exposures due to a high correlation between outdoor LAN and air pollution in our data. Future studies with a larger dataset could be instrumental in disentangling and investigating the independent effects of outdoor LAN and air pollution exposures on breast cancer risk and their potential interactions.

The sensitivity analyses indicated a higher risk for women living in non-rural areas. This finding suggests that exposure to outdoor LAN may be a more significant issue in urban areas, where numerous sources contribute to higher exposure to outdoor LAN.

For the effect modification by menopausal status, our findings were similar to some studies that also provided no evidence for effect modification^{182,199,205} but in contradiction to some that suggested a higher risk for pre-menopausal women^{200,203}.

Although many studies have reported that night shift work is associated with increased breast cancer risk^{95,158,163,227}, our study provided no such evidence based on small numbers of night-shift workers, thus the need to interpret the results cautiously. Nevertheless, this result is comparable to the results from the Danish Nurses Cohort with a larger sample size (n=27,713)¹⁹⁹. However, it is essential to acknowledge that night shift work results in a composite exposure to occupational factors, extreme levels of indoor and outdoor light, and other factors of circadian disruption, such as altered meals and sleep schedule^{138,228}. Therefore, in light of these multiple exposures among night shift workers, the potential circadian disruption attributable to outdoor LAN may be less pronounced or difficult to detect.

A higher OR for HER2+ breast tumors than for other subtypes in our study is a new finding. These results contradict the MCC Spain study ¹⁸², the only previous study to report findings for the HER2+ subtype, which found a null association for this tumor subtype. A few studies have previously examined the association with ER or PR status and have shown that melatonin suppression results in the proliferation of both types of tumors ^{199,200,202,203}. However, the mechanism behind this newly found association with the HER2+ tumor subtype in the present study is unknown.

5.3. Residual confounding

Our study did not explore the effect of indoor exposure or the use of electronic devices, indoor lighting, and sleep settings despite their substantial role in overall LAN exposure. Several case-control studies ^{158,207–209,212} assessed exposure to indoor LAN using interviews on sleep habits (such as using lights, curtains/blinds/shutters or electronic devices, or visibility at night) but provided conflicting results. Only a few studies have measured indoor and outdoor LAN ^{182,200,201,207}. Garcia-Saenz et al. mutually adjusted for indoor and outdoor exposure along with other confounders ¹⁸² and reported a noteworthy association between breast cancer and outdoor LAN for the blue light spectrum of light. Further studies could benefit from precise measurements of outdoor and indoor exposure using sensor-based measurements of indoor LAN, considering the use of electronic devices at night and sleep habits of using curtains/blinders/sleep masks, which can cancel out outdoor exposure. Such precise measurements could help to estimate the intensity and amount of outdoor LAN that penetrates the sleeping area and assess the risk attributable to each type of exposure.

Additionally, our analyses adjusted for education as a crude proxy for SES, which may have only partially addressed the confounding by SES. As socioeconomic status has been linked with a higher risk of breast cancer ²²⁹, further analyses could benefit from a more comprehensive measurement of SES.

5.4. Strengths and limitations

A notable strength of this study is the 10-year assessment of outdoor LAN exposure prior to the recruitment in the study, factoring in the residential history and the fluctuations in the level of exposure. Some studies have used the information on the residential history in

outdoor LAN assessment^{182,199,200,203,206} while others have considered a single assessment of exposure²⁰⁰ or assessment at a single address¹⁸².

The dataset for this study was also large enough to provide adequate information on multiple potential risk factors for breast cancer. This availability of information allowed our risk estimate to be adjusted on multiple confounders identified by DAG for the association of breast cancer and LAN exposure. However, as mentioned earlier, residual confounding could not be eliminated as we had no information on indoor exposure or other urban-environmental exposures. We attempted to account for confounding by air pollutants such as NO₂, PM_{2.5}, and PM₁₀ but not for other environmental factors, such as proximity to green spaces, which possibly correlate negatively with outdoor LAN exposure. Residential greenness is another important environmental factor that should be considered in future studies on outdoor LAN exposure. Residual confounding arising from unassessed variables such as indoor exposure and residential greenness remained.

The DMSP images used in our study have several limitations, including low resolution and no differentiation between the spectral components of the light. LAN assessment derived from DMSP data has also been criticized for the problem of saturation and inability to capture individual-level exposure, which leads to a risk of collinearity with other urban factors such as air pollution^{179,181}. It is also criticized for possible exposure misclassification, especially in urban areas, where the DMSP images do not provide enough variation²³⁰. Meanwhile, the ISS images used by Garcia-Saenz et al.¹⁸² facilitate a more elaborate evaluation of exposure to outdoor LAN. The ISS images offer a higher resolution (i.e., 30 m in urban areas) compared to ~650 m for the radiance-calibrated DMSP data in the present study; ISS images provide information on three spectral bands of visible light (red, green, blue). Our study could not use ISS images to assess exposure to blue light due to their unavailability during the study period, i.e., 2005-2007. Further studies employing ISS images would be valuable in further examining the association of breast cancer with blue light exposure.

In order to capture all incident breast cancers in the study area, the CECILE study employed exhaustive recruitment. The number of cases identified in *Ille-et-Vilaine* closely matched expected figures based on national incidence rates²³¹, while cases in *Côte d'Or* were recruited mainly from the area's main cancer hospital. Not all eligible cases and controls were selected,

which is typical of population-based case-control studies²³². Information on non-respondents was unavailable; thus, there is a possibility of selection bias and limited generalizability as the comparability of the study sample and study population could not be ascertained. Potential selection bias due to differential participation rates among controls was reduced by recruiting controls based on quotas of SES. Potential errors from selection bias might have occurred as cases were more frequently selected from urban areas. This potential bias was minimized by adjusting for the degree of urbanization at recruitment in the models, which accounts for, at least partially, the probability of selection of cases from urban areas rather than rural areas. Any recall biases inherent to the study design could not be ruled out.

5.5. Conclusion

Overall, this population-based case-control study found a suggestive association between exposure to outdoor LAN and breast cancer risk and indicated a weak association among urban residents. A stronger association was found for HER2+ type cancer than among other tumor subtypes. There was scarce evidence on effect modification by menopausal status, night shift work, or BMI. Further large-scale studies using more precise exposure assessments in indoor and outdoor settings and accounting for other environmental exposures, such as noise pollution and green spaces, are warranted to examine this association closely.

**CHAPTER 3: OUTDOOR LIGHT AT NIGHT AND BREAST CANCER RISK IN
E3N-GENERATIONS COHORT**

1. STUDY OBJECTIVE

This chapter investigates the association between exposure to artificial light at night (LAN) and breast cancer risk within the E3N-Generations Cohort, a large, prospective study. The subsequent sections will detail methods and materials, including a description of the cohort, the nested case-control study design, data collection processes, and analysis techniques. Results will be presented and discussed in the context of existing research, focusing on elucidating potential mechanisms linking LAN exposure and breast cancer risk.

2. METHODS AND MATERIALS

2.1. The E3N-Generations cohort

We conducted a case-control study nested in the E3N-Generations cohort (*Etude Epidémiologique après de femmes de l'Education Nationale*). E3N-Generations cohort is an ongoing national prospective cohort study established in 1990 to investigate risk factors for cancer and other chronic conditions in women ²³³. Women in the cohort were recruited between June 1990 and November 1991. E3N is also the French part of the European Prospective Investigation on Cancer (EPIC), a large-scale European cohort study managed by IARC, encompassing nearly 500,000 participants across 10 countries ²³⁴. Women aged 40-65, residing in France and insured by national health insurance covering workers from the *Mutuelle Générale de l'Education Nationale* (MGEN) were eligible for recruitment. Of the 500,000 women contacted, 98,995 participated at the baseline by completing a self-administered questionnaire on lifestyle, reproductive factors, anthropometry, medical history, family history of cancer, and signing an informed consent.

The study was approved by the French National Commission for Data Protection and Privacy. Informed consent was obtained from all individual participants included in the study.

2.1.1. Data collection in E3N-Generations Cohort

At inclusion in the cohort, women completed a self-administered questionnaire. Follow-up questionnaires were sent every 2-3 years by postal mail. So far, 12 questionnaires have been sent with an approximately 83% participation rate. All the questionnaires are available on the cohort's website (www.e3n.fr). Blood samples were collected from around 25,000 women from

1994 to 1999, and saliva samples were collected from an additional 47,000 women from 2008 to 2011.

Sociodemographic characteristics

At the inclusion, the information on date of birth, educational attainment, and occupational status was collected through the self-administered questionnaires. Information on urban-rural status was collected at the time of inclusion in the cohort and collected through information on residential addresses during the follow-up questionnaires.

Medical, reproductive, and lifestyle-related characteristics

Information on personal medical history and family history of cancer was collected during the interviews, along with information on hormonal and reproductive factors such as age at menarche and menopause, oral contraceptive use, menopausal status, menopausal hormonal therapy (MHT) use, history of gynecological diseases and surgeries (hysterectomy, oophorectomy), outcomes of each pregnancy, duration of breastfeeding and infertility treatment at inclusion in the cohort as well as during the follow-up.

Information on lifestyle-related factors such as alcohol consumption, smoking, recreational physical activities, dietary habits, height, and weight were also collected at inclusion and follow-up.

2.2. The nested case-control study

The present case-control study nested in the E3N-Generations cohort is a subset of women with completed residential addresses at baseline living in the metropolitan French territory (except Corsica) during the 1990-2011 follow-up period ²³⁵.

2.2.1. Recruitment of cases and controls

A total of 6,298 incident cases of invasive breast cancer cases were diagnosed from the inclusion in the cohort to the 10th questionnaire (2011). The breast cancer was self-reported in each questionnaire, and a few additional cases of cancers were further identified from the MGEN insurance files or information on causes of death obtained from the National Service on Causes of Deaths (*CépiDC-Inserm*). Ninety-three percent of breast cancer cases were validated with pathology reports or other medical reports from medical practitioners detailing the tumor characteristics, including histological type and hormone receptor status. The

proportion of false-positive self-reports was low (<5%). Cases previously diagnosed with other cancers, Paget's disease and phyllodes tumors (n=19) were excluded.

Tumor characteristics, including histological type and hormone receptor status, were extracted from the pathological reports. When a woman was diagnosed with more than one tumor at the same time, we considered the characteristics of the more advanced breast cancer in terms of tumor-node-metastasis (TNM) stage or grade of differentiation if the TNM stages were the same.

Each case was individually matched to one control selected using incidence density sampling. For each case, a control was selected among women with no previous cancer at the case's date of diagnosis. The matching procedure depended on the presence or absence of a blood sample: cases with a blood sample (before diagnosis) were matched with controls who also had a blood sample (before the diagnosis of the matched case). Matching was based on age (± 1 year), residential area (French Departments), date (± 3 months), and menopausal status at the time of blood collection. In the absence of blood samples, the cases were matched to controls on the same criteria but at the time of inclusion in the cohort. Women with missing data on matching variables and their pair (3 pairs, n =6) and those with missing information on address or residing outside continental France (1,054 pairs, n= 2,108) were excluded, leaving 5,222 breast cancer cases and 5,222 controls.

The reference date was defined as the date of diagnosis for cases and the date of diagnosis of the corresponding matched pair for controls.

2.2.2. Geocoding of the residential history

The addresses of the subjects selected for the study were reported in the baseline (1990) and in the 5th to the 10th follow-up questionnaires (years 1997, 2000, 2002, 2005, 2008, and 2011). In the 3rd and the 4th follow-up questionnaires (years 1993 and 1995), only postal codes of participants were reported. If the addresses in the first and fifth questionnaires matched and corresponded to the postal codes for the third or fourth questionnaires, it was assumed that the participants did not move, and the address from the first questionnaire was assigned to the third and fourth questionnaires. If the postal codes corresponded to either the first or fifth questionnaire, the address from the corresponding questionnaire was assigned. Similar rules were applied to retrieve the missing addresses after the fifth questionnaire. If a complete

address could not be assigned or addresses were outside mainland France, the subjects were excluded from the study^{236,237}.

All the addresses of included women were geocoded using the ArcGIS Software (ArcGIS Locator version 10.0, Environmental System Research Institute – ESRI, Redlands, CA, USA) and the address database, BD Adresse®, from the National Geographic Institute. Detailed methods of address management and the geocoding process have been described elsewhere^{236,237}.

2.2.3. Outdoor LAN exposure assessment

Exposure to the outdoor LAN was assessed using the DMSP images, applying methods similar to those in the CECILE Study (See Chapter 2, section 2.5). For the study period 1990-2011, Table 10 shows the availability of the radiance-calibrated DMSP images, their temporal coverage, and their application for each study year. The radiance-calibrated images from DMSP were unavailable for all the study years; thus, the values from the closest year were applied for the years where the images were unavailable. The 1996 image was used for 1990 to 1997 (with an assumption that the street lighting remained relatively unchanged during this period), the 1999 image was applied to 1998, the 2003 image was used for 2002, the 2006 image was applied to 2005, 2007 and 2008, and the 2010 image was applied to 2009. These images were cross-referenced with geocoded locations of each address in a geographic information system software (GIS) – ArcGisPro 3.0, which provided the luminosity value at each location.

Table 10: Availability of radiance-calibrated images, their temporal range, and application in the case-control study nested within the E3N-Generations cohort, France 1990-2011.

Year	Temporal range	Study period
1996	March 16, 1996–February 12, 1997	1990-1997
1999	January 19 –December 11, 1999	1998-1999
2000	January 3 – December 29, 2000	2000-2001
2003	December 30, 2002–November 27, 2003	2002-2003
2004	January 18 –December 16, 2004	2004
2006	November 28, 2005–December 24, 2006	2005-2008
2010	January 11, 2010 - December 9, 2010	2009-2010
2011	January 11, 2011 -July 31, 2011	2011

For this nested case-control study, the exposure to outdoor LAN was calculated for all the cases and their matched controls from 1990 to 2011 using several exposure metrics as follows:

- i) Exposure at inclusion: For all women, exposure to outdoor LAN was calculated at the year of inclusion.
- ii) Cumulative exposure: For all women, the cumulative exposure was calculated as an average of annual exposures weighted on the duration of stay at each address.
- iii) Exposure at diagnosis: For all women, exposure to outdoor LAN was calculated at the year of the cases' diagnosis.
- iv) Exposure during 5 years before diagnosis: Among the subset of women with ≥ 5 years of LAN exposure data available ($n=9,182$), the average of annual exposures was calculated weighted on the duration of stay at each address.
- v) Exposure during 10 years before diagnosis: Among the subset of women with ≥ 10 years of LAN exposure data available ($n =6,781$), the average of annual exposures was calculated weighted on the duration of stay at each address.

2.2.4. Air pollution

Exposure to air pollution was assessed as average annual exposure to nitrogen dioxide (NO₂) and particulate matter (PM_{2.5} and PM₁₀) at the participant's residential addresses from 1990 through 2011. The exposure to the air pollutants was estimated using a land use regression (LUR) model and a chemistry transport model (CHIMERE) ²³⁸. Our analyses used mean annual NO₂, PM_{2.5}, and PM₁₀ concentration estimates ($\mu\text{g}/\text{m}^3$) at the residential address for the year of diagnosis.

2.2.5. Residential greenness

Residential greenness resulting from the presence of trees, gardens, or parks around the residential area is suggested to have a protective effect on breast cancer through enhancing mental health, promoting physical activities and social cohesion, and particularly by acting as a physical barrier in terms of outdoor LAN exposure, air pollution and so on ²³⁹. In our study, residential greenness was assessed using the Normalized Difference Vegetation Index (NDVI), a unitless indicator that assesses the vegetation functioning by comparing the values of absorptions and reflection of red to near-infrared parts of electromagnetic radiations ²⁴⁰. The values of NDVI range from -1 to +1, where values closer to -1 indicate the water bodies, values

closer to 0 indicate total urban spaces comprising roads, ground, stones, pavements, and buildings, whereas values closer to +1 indicate a healthy and higher density of plants and vegetation. NDVI was calculated using the images from the Landsat 5 satellite with a spatial resolution of ~30 m²⁴¹. The images from May 1 to July 31 were used as this is the period with the highest vegetation activity and lowest cloud coverage interference^{107,242}. We retrieved images from the Landsat satellites for 4 reference years, 1990, 2000, 2005, and 2010²⁴³. For the year 1990, we used data from 1990 and 1991; for 1995, we used the data from 1995 and 1996; for 2000, we used data from three years, 1999, 2000, and 2001 because of the cloud coverage issues; for 2005 we used the data of 2005 and 2006. Then, the image of 1990 was assigned to the geocoded locations for the years 1990-1993, the image of 1995 was assigned to the years 1994-1998, the image of the year 2000 was assigned to the years 1999-2003, the image of 2005 was assigned to the years 2004-2008, and the image of 2010 was assigned to the years 2009-2011. For our analyses, we used the mean values of NDVI within the 300 m buffer around the residential address of women at diagnosis.

3. ANALYTICAL STRATEGY

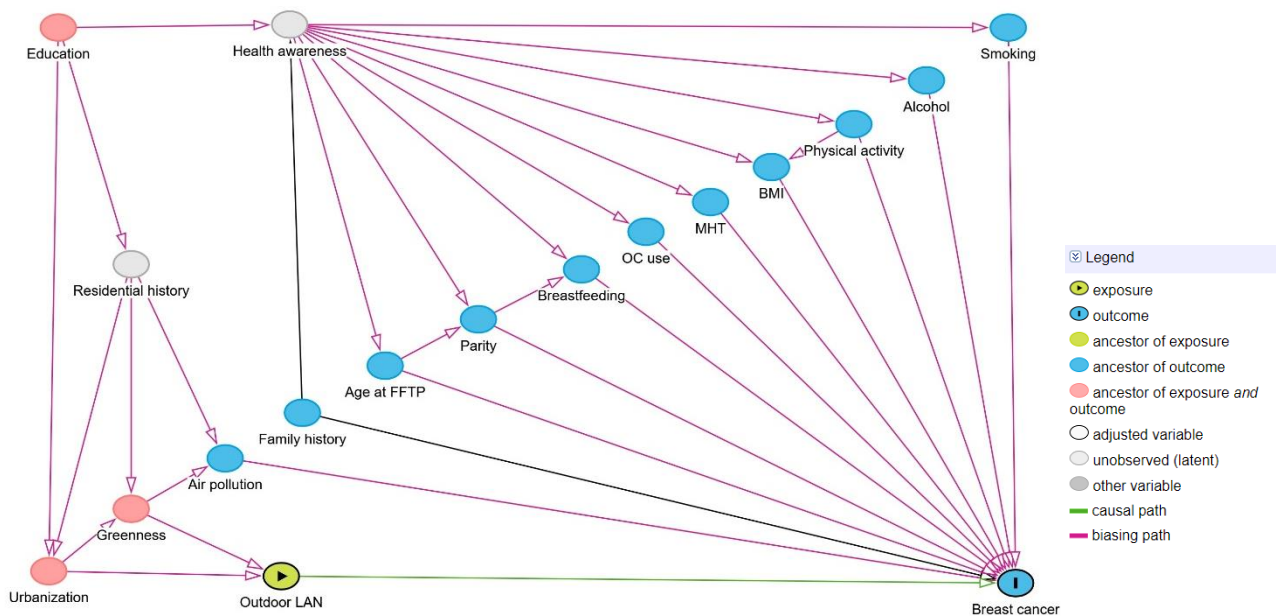
A series of statistical methods were applied to assess the association between exposure to outdoor LAN and breast cancer risk. Initially, descriptive statistics were used to characterize the study population, followed by exploring the exposure distribution among the study population. Finally, regression models were applied to obtain the risk estimates for this association while also assuring the robustness of the models.

3.1. Choice of covariates

The variables to be considered as potential confounders and included in the main analyses were selected using the Directed Acyclic Graph (DAG) approach^{199,220}. Potential covariates considered in this study are shown in Fig 17 which included age at reference, department of residence at reference, age at first full-term pregnancy, parity, menopausal status, oral contraceptive use, MHT use, family history of breast cancer in first-degree relatives, alcohol consumption, smoking, body mass index (BMI), recreational physical activity, night shift work, educational level (proxy for SES), occupation, urbanization of the residential area at reference, and exposure to air pollution. The matching factors of age and department of residence were forced into the DAG. The causal links between the covariates, outdoor LAN, and breast cancer

were drawn based on a priori information from available literature. DAG was drawn using the DAGitty software ²²¹.

Figure 17: Directed acyclic graph (DAG) for the association of outdoor LAN and breast cancer in the case-control study nested within the E3N-Generations cohort.



BMI: Body-mass Index, FFTP: First full-term pregnancy, LAN: Light at Night, MHT: Menopausal hormonal therapy, OC: Oral contraceptives

The minimal sufficient adjustment set identified using DAG was:

"Age at FFTP, Air pollution, Alcohol, BMI, Breastfeeding, Family history, MHT, OC use, Parity, Smoking"

This minimal adjustment set included a wide range of breast cancer risk factors that were adequately measured in our study and would reduce residual confounding. In addition to the potential confounders identified by DAG, we also adjusted for residential greenness in the models, considering the relevance of greenness in the context of outdoor LAN exposures.

3.1.1. Definition of covariates included in the analysis

Age

Age was one of the matching variables and was calculated using the date of birth for all participants and the date of reference for cases and controls. Age was adjusted for in all models as a continuous variable.

Department of residence

Study participants were selected from all over France. Department of residence was a matching variable.

Education level

Information on the highest education level attained was collected at the time of inclusion in the cohort and was categorized into three levels: ≤secondary, 1-2 year university degree, ≥ 3-year university degree.

Family history of breast cancer

Information on family cancer history among first-degree relatives was used as a binary variable (yes, no) in the models. First-degree relatives include parents, siblings, and children

223.

Parity and age at first full-term pregnancy

Parity is defined as the number of full-term pregnancies and was determined using pregnancy information collected from a self-administered questionnaire at the time of inclusion in the cohort, along with the age at first full-term pregnancy. Parity and age at first full-term pregnancy were used as a combined variable with 3 categories of parity and age at first full-term pregnancy: nulliparous, 0-2 children and <30 years at first full-term pregnancy, 0-2 children and ≥30 years at first full-term pregnancy.

Oral contraceptives

Oral contraceptive use was categorized as a binary variable: ever, never.

Breastfeeding

Breastfeeding information was collected at the time of inclusion and used as a categorical variable of ever or never breastfeeding.

Menopausal status and menopausal hormonal therapy use

Information on menopausal status was collected at the time of inclusion in the study and during follow-up. Menopausal status at inclusion was a matching variable. Menopausal hormonal therapy included estrogen-only or estrogen-progesterone treatments among post-menopausal women. In the main analysis, a combined variable of menopausal status and MHT was used with three categories: pre-menopausal women, post-menopausal women with MHT use, and post-menopausal without MHT use at the reference date.

Alcohol consumption

Alcohol consumption was quantified using grams of alcohol consumed per day, and the information was collected at the inclusion in the cohort as well as during the follow-up. This variable was divided into <10 gr/day and ≥ 10 gr/day based on the median value of their distribution.

Tobacco consumption

Tobacco smoking was used as a categorical variable with 3 categories: non-smokers, former smokers, and current smokers.

Body mass index

BMI at diagnosis was calculated from height and weight information gathered during inclusion and follow-up. The WHO's BMI classification created the BMI variable: <18.5 , $18.5-24.9$, $25-29.9$, and ≥ 30 kg/m². In the models, BMI was used at the year of diagnosis.

Urbanization level

Urbanization of the residential area was determined using residential addresses at inclusion and during the follow-up in the cohort. In the analyses, urban-rural status at the reference date was used in two categories of urban or rural areas.

Air pollution

Exposure to air pollution was assessed as average annual exposure to nitrogen dioxide (NO₂) and particulate matter (PM_{2.5} and PM₁₀) at the participant's residential addresses from 1990 through 2011. The exposure to the air pollutants was estimated using a land use regression (LUR) model and a chemistry transport model (CHIMERE) ²³⁸. Our analyses used mean annual NO₂, PM_{2.5}, and PM₁₀ concentration estimates (µg/m³) at the residential address at the reference date.

Residential greenness

For our analyses, we used the mean values of NDVI within the 300 m buffer around the residential address of women at the reference date.

3.2. Statistical methods

A descriptive comparison was made between cases and controls for their sociodemographic, reproductive, hormonal, lifestyle-related characteristics and other environmental exposures using chi-square tests for categorical variables and Wilcoxon signed-rank tests for continuous variables at a statistical significance level of $p = 0.05$. For the primary analyses of the association between exposure to outdoor LAN and breast cancer risk, conditional logistic regression models were used to calculate the odds ratios (ORs) of association between exposure to outdoor LAN and breast cancer to account for the 1:1 matched pair of cases and controls. The models were conditioned on the matching factors: age, date, department of residence, menopausal status at blood collection or inclusion, as explained above, and biological samples (blood, saliva, none). Odds ratios with 95% confidence intervals (CIs) were calculated for higher quartiles (Q) of LAN exposure (Q2, Q3, and Q4) with reference to Q1 and for one interquartile range increase in LAN exposure (IQR = 216.26 nW/cm²/sr) based on the distribution of exposure among controls only.

We applied conditional logistic regression models in multiple steps to achieve adjustment of the potential covariates as well as to carefully examine the effect of important environmental covariates in the association between exposure to outdoor LAN and breast cancer risk. The adjustments were achieved in the following order:

Model 1: Adjusted for age at reference (continuous)

Model 2: Further adjusted for reproductive and hormonal factors, including parity and age at first full-term pregnancy, breastfeeding at inclusion, history of breast cancer among 1st-degree relatives at inclusion, use of oral contraceptive pills at diagnosis, menopausal status

and menopausal hormonal therapy (MHT) used at diagnosis, lifestyle-related factors including BMI, alcohol consumption, tobacco smoking, and education.

Model 3: Further adjusted for different air pollutants alternatively (NO₂ or PM_{2.5}, or PM₁₀ at diagnosis in continuous form) or residential greenness (NDVI at 300m buffer)

Model 4: Model 2 further adjusted for air pollution (NO₂) and residential greenness (NDVI at 300m buffer)

In our analyses, we assessed the possible correlation between outdoor LAN, air pollution, and residential greenness, which can occur concurrently. The Pearson correlation coefficient was used to assess this correlation between exposure to outdoor LAN and air pollutants. Additionally, possible collinearity between these exposures while using them in the same regression model was assessed using the variance inflation factor (VIF) in Model 4. The VIF indicated collinearity if greater than 5²²⁶.

Missing values of less than 5% were replaced with median values for continuous variables and modal values for categorical variables, and more than 5% of missing values for any categorical variables were included as a separate category.

Subgroup analyses were conducted for different hormone receptor statuses of the breast tumors: Estrogen Receptor (ER) positive, ER-negative, Progesterone Receptor (PR) positive, PR negative, Hormone receptor negative (ER- and PR-), and Hormone receptor-positive (ER+ or PR+)

3.2.1. Stratified analyses

Stratified analyses were conducted for menopausal status at diagnosis to explore the differential effect of outdoor exposure to LAN among pre- and post-menopausal women, considering the varying levels of hormonal activities and susceptibility of breast tissues to possible carcinogens.

Urban areas are expected to have multiple sources of outdoor LAN, leading to varying exposure levels between urban and rural areas. To explore the effect of this variation, we assessed the possible effect modification of the association by urban-rural status. Additionally, considering that urban areas have more varying, typically lower levels of residential greenness and higher air pollution than rural areas, we further assessed if different levels of greenness

or air pollution would change the association between outdoor LAN and breast cancer risk. Restricting to the urban resident, we stratified the analysis by levels of residential greenness and air pollutants. The categories were created as urban areas with high or low greenness using median NDVI at diagnosis as the cutoff value (based on the distribution among controls in urban areas). Similarly, categories were created as low and high air pollution using median values of each air pollutant as cut-off (based on the distribution among controls in urban areas).

Due to the stratification, the matched pairs of cases and controls could not be maintained; thus, unconditional logistic regression models adjusting for the matching factors (age, menopausal status at inclusion, and department of residence at inclusion) and other selected covariates.

3.2.2. Sensitivity analyses

Sensitivity analyses were conducted using the LAN exposure at inclusion, cumulative average exposure for all women, and the average exposure of LAN during the 5 and 10 years before diagnosis, restricted to women with at least 5 and 10 years of exposure information, respectively.

In the previous chapter, due to instrumental errors, women with outlying values of LAN were excluded from the main analysis of the association between outdoor LAN and breast cancer risk. In this nested case-control study, 582 women (5.6%, 327 cases, and 225 controls) had extreme LAN values. Given this considerable proportion, these values were not excluded from the primary analysis. A sensitivity analysis was conducted to compare the potential differences in results when the outlying values were omitted.

We also estimated the minimum detectable ORs for this study. Estimations of the minimum detectable OR in this study can be found in Annex 4.

All statistical analyses were performed using SAS software version 9.

4. RESULTS

4.1. Descriptive characteristics

The study sample comprised 5,222 cases and 5,222 individually matched controls. Table 11 compares sociodemographic, reproductive, hormonal, and lifestyle-related characteristics between cases and controls. The distribution of cases and controls by the year of diagnosis can be found in Annex 10.

4.1.1. Sociodemographic and personal characteristics

The distribution of cases and controls across age categories at the reference date was similar. Cases were more likely to have higher levels of educational attainment (36.8%) compared to the controls (33.1%). Cases were also more likely than controls to have a history of benign breast disease or have a history of breast cancer among 1st-degree relatives.

4.1.2. Reproductive and hormonal characteristics

The mean age distribution at menarche, breastfeeding, ever use of oral contraceptives, and menopausal status among cases and controls were very comparable. However, more cases than controls tended to be nulliparous (12.9% vs. 10.8%) to have their first full-term pregnancy at age 30 years or later (15% vs. 12%).

4.1.3. Lifestyle-related characteristics

Cases and controls had similar BMIs as well as tobacco smoking status, while more cases (28.7%) consuming >10 grams of alcohol per day compared to the controls (11.5%).

4.1.4. Environmental exposures

Cases were more likely than controls to live in urban areas with lower greenness at the reference date. The exposure to air pollution (NO₂, PM_{2.5}, and PM₁₀) and residential greenness (NDVI) were similar among cases and controls.

Odds ratios and their corresponding 95% confidence intervals for the association of these variables with the breast cancer risk independent of the exposure in this study can be found in Annex 11.

Table 11: Descriptive characteristics of the study participants in the case-control study nested within the E3N-Generations cohort, 1990-2011.

	Total n=10444	Cases n=5222	Controls n=5222	p-values †
Sociodemographic and personal characteristics				
Age at diagnosis (yrs)				
Mean ± SD	60.6 ± 8.1	60.6 ± 8.1	60.6 ± 8.1	0.95
10 years age groups				
40-50 yrs	1076	538 (10.3)	538 (10.3)	0.99
50-60 yrs	3889	1950 (37.3)	1939 (37.1)	
60-70 yrs	4107	2047 (39.2)	2060 (39.5)	
70-80 yrs	1291	646 (13.4)	645 (12.3)	
80-90 yrs	81	41 (0.8)	40 (0.8)	
Education level, n(%)				
≤Secondary education	1676	802 (15.4)	874 (16.7)	<0.001
1-2 year university degree	5118	2497 (47.8)	2621 (50.2)	
≥3 year university degree	3650	1923 (36.8)	1727 (33.1)	
History of breast cancer among 1st degree relatives, n(%)				
No	9003	4336 (83.0)	4997 (89.4)	<0.0001
Yes	1441	886 (17.0)	555 (10.6)	
Personal history of benign breast disease, n(%)				
Never	7733	3688 (70.6)	4045 (77.5)	<0.0001
Ever	2711	1534 (29.4)	1177 (22.5)	
Reproductive and hormonal characteristics				
Age at menarche				
Mean ± SD	12.8 ± 1.4	12.8 ± 1.4	12.8 ± 1.4	0.08
In categories, n(%)				
<12 years	2148	1098 (21.0)	1050 (20.1)	0.38
12-14 years	5406	2704 (51.8)	2702 (51.7)	
≥14 years	2890	1420 (27.2)	1470 (28.2)	
Parity n(%)				
Nulliparous	1236	674 (12.9)	562 (10.8)	<0.0001
1 or 2	6299	3198 (61.2)	3101 (59.4)	
≥3	2909	1350 (25.9)	1559 (29.8)	
Age at first full-term pregnancy ^a				
<30 yrs	7968	3867 (85.0)	4101 (88.0)	<0.0001
≥30 yrs	1240	681 (15.0)	559 (12.0)	
Breastfeeding at least 1 child, n(%) ^a				
Never	3520	1709 (37.6)	1811 (38.9)	0.21
Ever	5688	2839 (62.4)	2849 (61.1)	
Oral contraceptive use, n(%)				
Never	4305	2147 (41.1)	2158 (41.3)	0.83
Ever	6139	3075 (58.9)	3064 (58.7)	
Menopausal status, n(%)				
Pre-menopausal	1680	874 (16.7)	806 (15.4)	0.07
Post-menopausal	8764	4348 (83.3)	4416 (84.6)	

	Total n=10444	Cases n=5222	Controls n=5222	p-values †
Menopausal hormonal therapy, n(%)^b				
No	2567	1177 (27.1)	1390 (31.5)	<0.0001
Yes	5974	3062 (70.4)	2912 (65.9)	
Missing	223	109 (2.5)	114 (2.6)	
Lifestyle-related characteristics				
BMI, n(%)				
<18.5 kg/m ²	299	142 (2.7)	157 (3.0)	0.09
18.5 – 24.9 kg/m ²	7193	3553 (68.0)	3640 (69.7)	
25-29.9 kg/m ²	2316	1210 (23.2)	1106 (21.2)	
≥30 kg/m ²	636	317 (6.1)	319 (6.1)	
Alcohol consumption, n(%)				
Never	2434	1116 (21.4)	1197 (22.9)	0.02
>0-10 grams per day	3203	1608 (30.8)	1640 (31.4)	
>10 grams per day	2868	1502 (28.7)	1359 (11.5)	
Missing	1939	996 (19.1)	1026 (19.7)	
Smoking, n(%)				
Current smokers	885	441 (8.4)	444 (8.5)	0.57
Former smokers	3443	1755 (33.6)	1688 (32.3)	
Non-smokers	5032	2489 (47.7)	2543 (48.7)	
Missing	1084	537 (10.3)	547 (10.5)	
Environmental exposures				
NDVI within 300 m buffer				
Mean ± SD	0.51 ± 0.15	0.51 ± 0.15	0.52 ± 0.15	0.06
Urbanization, n(%)				
Rural	1768	346 (16.2)	922 (17.7)	0.03
Urban				
Urban with low greenness	5132	2627 (50.3)	2505 (48.0)	
Urban with high greenness	3544	1749 (33.5)	1795 (33.5)	
Air pollution				
NO₂				
Mean ± SD	13.4 ± 11.6	13.5 ± 11.7	13.3 ± 11.5	0.27
<Median (10.3 µg/m ³)	5166	2555 (48.9)	2611 (50.0)	
≥Median (10.3 µg/m ³)	5278	2667 (51.1)	2611 (50.0)	
PM_{2.5}				
Mean ± SD	10.6 ± 7.4	10.6 ± 7.4	10.5 ± 7.4	0.95
<Median (9.6 µg/m ³)	5225	2614 (50.1)	2611 (50.0)	
≥Median (9.6 µg/m ³)	5219	2608 (49.9)	2611 (50.0)	
PM₁₀				
Mean ± SD	14.8 ± 10.2	14.9 ± 10.2	14.8 ± 10.2	0.80
<Median (13.5 µg/m ³)	5211	2599 (49.8)	2612 (50.0)	
≥Median (13.5 µg/m ³)	5233	2623 (50.2)	2610 (50.0)	

BMI: Body-mass Index, NO₂: nitrogen dioxide, PM: particulate matter

a: among parous women only, b: among post-menopausal women only, †: p-values derived from Wilcoxon signed-rank test for continuous variables and chi-square test for categorical variables

4.2. Distribution of outdoor LAN using different exposure metrics

Table 12 shows the distribution of exposure to outdoor LAN assessed at different time points such as at reference, at inclusion, during the whole study period (cumulative average exposure), and during the preceding 5 or 10 years before diagnosis among controls. The exposure at inclusion and reference reflects exposure at a single time point, while the cumulative average exposure covers the period ranging from 1 to 21 years. The metrics for 5 and 10 years prior to diagnosis captured the exposure during those specific periods before, regardless of the year of diagnosis, ensuring all women have the same exposure period. Despite this heterogeneity in the duration of exposure between these exposure metrics, they were found to be highly correlated with one another (Table 13). The comparison of these metrics (Table 12) showed that the LAN exposure at the reference date was higher than LAN exposure at inclusion or the cumulative average exposure, reflecting an increase in outdoor LAN exposure over time. The overall trend of annual exposures increased from 1990 to 2008, with some decrease from 2009 to 2011. The overall annual averages were higher in urban and rural areas across all the study years. The line charts and tables showing mean annual exposures to outdoor LAN among controls and by urban-rural status may be found in Annex 12.

Table 12: Distribution of outdoor LAN exposure (nW/cm²/sr) among controls (n =5222) using different measurement metrics in the case-control study nested within the E3N-Generations cohort, 1990–2011.

	Mean ± SD	Median (Q1- Q3)	Min-Max
At inclusion	165.9 ± 191.5	89.3 (29.4-238.1)	0.0-1144.6
At reference	199.2 ± 237.2	110.3 (29.5-290.7)	0.0-2021.6
Cumulative average	187.8 ± 214.3	104.9 (34.0-269.3)	0.0-1378.7
5 years before diagnosis, ^a	205.9 ± 252.2	110.0 (29.4-297.4)	0.0-2187.9
10 years before diagnosis ^b	193.3 ± 237.6	99.9 (27.9-279.6)	0.0-2150.9

a: restricted to women with at least 5 years of exposure information available (n=4591)

b: restricted to women with at least 10 years of exposure information available (n= 3438)

Table 13: Correlation matrix (Pearson correlation coefficient and p-values) for different LAN measurement metrics among controls only in the case-control study nested within the E3N-Generations cohort, 1990–2011.

	At inclusion ^a	At reference ^a	Cumulative average ^a	5 years before diagnosis ^b	10 years before diagnosis
At inclusion ^a	1.00				
At reference ^a	0.68, p <.0001	1.00			
Cumulative average ^a	0.79, p <.0001	0.91, p <.0001	1.00		
5 years before diagnosis ^b	0.72, p <.0001	0.95, p <.0001	0.97, p <.0001	1.00	
10 years before diagnosis ^c	0.74, p <.0001	0.91, p <.0001	0.99, p <.0001	0.98, p <.0001	1.00

a: among all controls (n=5222), b: restricted to women with at least 5 years of exposure information available (n=4591), c: restricted to women with at least 10 years of exposure information available (n=3438)

The distribution of outdoor LAN exposure at the reference year by various variables of interest can be found in Annex 13. Outdoor LAN exposure was found to be higher among post-menopausal women than in pre-menopausal women. Women with higher educational attainment and those with higher exposure to air pollution were likelier to have higher exposure to outdoor LAN.

4.3. Association between outdoor LAN and breast cancer risk

The odds ratios for the association between exposure to outdoor LAN and breast cancer risks from the conditional logistic models are detailed in Table 14. Model 1, conditioned for the matching factors, shows a regular increase in the ORs in the 2nd, 3rd, and 4th quartiles with reference to the lowest quartile, with an OR in the 4th quartile of 1.20 (95% CI: 1.06-1.37). Adjustment for reproductive, hormonal, and lifestyle-related factors and education in Model 2 resulted in a reduction in the ORs. No further reduction of the ORs was observed in Models 3a, adjusted for NO₂. We alternatively adjusted for PM_{2.5} and PM₁₀ and found negligible differences in the estimates. The models adjusting for PM_{2.5} and PM₁₀ can be found in Annex 14.

Further, in Model 3b, we adjusted for residential greenness instead of air pollution and observed a negligible reduction in the ORs across the quartiles. In Model 4, both NO₂ and NDVI were adjusted for and no changes in the estimates were observed. The ORs per one IQR increase in outdoor LAN exposure were significantly elevated in Models 3a adjusted for NO₂ (1.11, 95% CI: 1.04-1.18) and in Model 4 adjusted for NO₂ and NDVI (1.12, 95% CI: 1.03-1.21).

4.4. Effect modification of the association between outdoor LAN and breast cancer risk

Table 15 shows the stratified analysis by menopausal status, urbanization, and levels of greenness and air pollution among urban residents using conditional logistic regression models. There was no significant effect modification by menopausal status, urbanization, greenness, or air pollution levels. However, the OR tended to be higher across all models in post-menopausal (e.g., Model 3a OR: 1.10, 95% CI: 1.02-1.18) than in pre-menopausal women.

Stratified analyses restricted to women residing in urban areas showed that among those who resided in areas with lower greenness, the ORs tended to be higher across all models than those in urban areas with higher greenness. In contrast, those with higher levels of air pollution exhibited similar ORs compared to those with lower air pollution levels in urban areas.

4.5. Association between outdoor LAN and breast cancer risk by hormone receptor status

In Table 16, we explored the association of outdoor LAN exposure with tumor subtypes defined by the hormone receptor status. We found slightly elevated ORs for hormone receptor-positive (ER+ and ER+/PR+) and progesterone receptor-negative (PR-) tumors in the fully adjusted models (Model 4).

Table 14: Odds ratio and 95% confidence intervals for the association between outdoor LAN and breast cancer risk, adjusting for different covariates in the case-control study nested within the E3N-Generations cohort, 1990-2011.

Outdoor LAN (nW/cm ² /sr)	Cases, n (%)	Controls, n (%)	Model 1	Model 2	Model 3a: Model 2+ NO ₂	Model 3b: Model 2 + NDVI	Model 4: Model 2 + NO ₂ + NDVI
			OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Q1 (0-29.5)	1038 (22.6)	1306 (25.0)	Ref	Ref	Ref	Ref	Ref
Q2 (29.6-110.3)	1298 (24.9)	1305 (25.0)	1.09 (0.97-1.22)	1.07 (0.95-1.20)	1.07 (0.95-1.20)	1.06 (0.94-1.20)	1.06 (0.94-1.19)
Q3 (110.4-290.7)	1341 (25.7)	1306 (25.0)	1.14 (1.02-1.28)	1.11 (0.99-1.25)	1.11 (0.98-1.26)	1.09 (0.95-1.25)	1.09 (0.95-1.25)
Q4 (290.8-2021.6)	1375 (26.3)	1305 (25.0)	1.20 (1.06-1.37)	1.13 (0.99-1.29)	1.12 (0.96-1.31)	1.10 (0.92-1.31)	1.10 (0.91-1.32)
Per IQR increase	5222	5222	1.12 (1.06-1.18)	1.09 (1.03-1.15)	1.11 (1.04-1.18)	1.11 (1.03-1.19)	1.12 (1.03-1.21)

IQR = 261.26 nW/cm²/sr based on the distribution of LAN among controls only

Model 1: adjusted for age at reference

Model 2: further adjustment on reproductive and hormonal factors (parity, age at first full-term pregnancy, breastfeeding, oral contraceptive use, history of breast cancer among 1st-degree relatives, menopausal status at diagnosis, and menopausal hormonal therapy use), lifestyle-related factors at diagnosis (BMI, smoking and alcohol consumption), and education

Model 3: Model 2 + further adjustment on air pollution (NO₂) or residential greenness (NDVI at 300m buffer)

Model 4: Model 3a + further adjustment on residential greenness (NDVI at 300m buffer)

Table 15: Odds ratio and 95% confidence for the effect modification of the association between outdoor LAN and breast cancer risk adjusting for different covariates in the case-control study nested within the E3N-Generations cohort, 1990-2011.

	N	Model 1	Model 2	Model 3a: Model 2+NO₂	Model 3b: Model 2 + NDVI	Model 4: Model 2 + NO₂+ NDVI	P for interact ion
Per IQR increase^a	cases/controls	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	
Menopausal status							
Pre-menopausal ^b	874/806	1.04 (0.89-1.22)	1.00 (0.85-1.18)	1.00 (0.84-1.18)	0.98 (0.80-1.20)	0.97 (0.79-1.19)	0.85
Post-menopausal	2091/2078	1.13 (1.05-1.18)	1.10 (1.03-1.18)	1.10 (1.03-1.18)	1.10 (1.02-1.19)	1.10 (1.02-1.19)	
Urbanization							
Rural^c	846/922	1.05 (1.01-1.10)	1.06 (1.02-1.10)	1.06 (1.02-1.10)	-	-	0.05
Urban	4376/4300	1.09 (1.02-1.16)	1.06 (0.99-1.13)	1.06 (0.99-1.13)	-	-	
Low NDVI <0.49 ^d	2235/2151	1.10 (1.02-1.19)	1.08 (1.00-1.17)	1.08 (1.00-1.17)	-	-	0.10
High NDVI ≥0.49	2141/2149	1.02 (0.88-1.18)	0.95 (0.82-1.11)	0.99 (0.81-1.11)	-	-	
Low NO ₂ (<11.4 µg/m ³) ^d	2194/2150	1.10 (1.00-1.21)	1.07 (0.97-1.19)	-	1.05 (0.93-1.18)	-	0.47
High NO ₂ (≥11.4 µg/m ³)	2182/2150	1.08 (1.00-1.16)	1.04 (0.96-1.13)	-	1.08 (0.98-1.19)	-	
Low PM _{2.5} (<10.0 µg/m ³) ^d	2213/2151	1.10 (1.01-1.21)	1.07 (0.98-1.18)	-	1.05 (0.94-1.17)	-	0.36
High PM _{2.5} (≥10.0 µg/m ³)	2163/2149	1.07 (0.99-1.16)	1.04 (0.96-1.13)	-	1.08 (0.97-1.19)	-	
Low PM ₁₀ (<14.0 µg/m ³) ^d	2193/2150	1.10 (1.00-1.20)	1.07 (0.97-1.17)	-	1.05 (0.94-1.17)	-	0.42
High PM ₁₀ (≥14.0 µg/m ³)	2183/2150	1.08 (0.99-1.17)	1.04 (0.96-1.14)	-	1.08 (0.98-1.19)	-	

Model 1: adjusted for age at reference (continuous), menopausal status at inclusion, department of residence

Model 2: further adjustment on reproductive and hormonal factors (parity, age at first full-term pregnancy, breastfeeding, oral contraceptive use, history of breast cancer among 1st-degree relatives, menopausal status at diagnosis, and menopausal hormonal therapy use), lifestyle-related factors at diagnosis (BMI, smoking and alcohol consumption), and education

Model 3: Model 2 + further adjustment on air pollution (NO₂) or residential greenness (NDVI at 300m buffer)

Model 4: Model 3a + further adjustment on residential greenness (NDVI at 300m buffer)

a: IQR= 261.26 nW/cm²/sr based on the distribution of LAN among all controls, b: not adjusted for menopausal hormonal therapy use, c: IQR= 10.26 nW/cm²/sr based on the distribution of LAN among controls in rural areas only, d: cutoff used for is median based on distribution in controls living in urban areas(Median NDVI = 0.49, Median NO₂ = 11.4 µg/m³, Median PM_{2.5} = 10.0 µg/m³, Median PM₁₀ = 14.0 µg/m³)

Table 16: Odds ratio and 95% confidence intervals for the association between outdoor LAN and different breast tumor subtypes adjusting for different covariates in the case-control study nested within the E3N-Generations cohort, 1990–2011.

	N	Model 1	Model 2	Model 3a: Model 2+NO₂	Model 3b: Model 2 + NDVI	Model 4: Model 2 + NO₂+ NDVI
Per IQR increase	Cases/controls	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
ER/ PR receptor status						
ER-	757/757	1.04 (0.92-1.19)	1.06 (0.92-1.21)	1.04 (0.88-1.23)	1.05 (0.88-1.25)	1.03 (0.85-1.26)
ER+	3399/3399	1.14 (1.04-1.19)	1.07 (1.00-1.15)	1.08 (1.00-1.17)	1.09 (1.00-1.20)	1.10 (1.00-1.21)
PR-	1437/1437	1.08 (0.98-1.19)	1.05 (0.95-1.16)	1.05 (0.93-1.19)	1.12 (0.98-1.28)	1.11 (0.96-1.28)
PR+	2595/2595	1.10 (1.01-1.19)	1.06 (0.98-1.15)	1.08 (0.98-1.19)	1.07 (0.96-1.18)	1.08 (0.96-1.21)
ER- and PR-	609/609	1.11 (0.98-1.26)	1.04 (0.89-1.221)	1.08 (0.92-1.28)	1.07 (0.88-1.30)	1.06 (0.85-1.32)
ER+ or PR+	3542/3542	1.11 (1.04-1.18)	1.07 (1.00-1.15)	1.08 (0.99-1.17)	1.08 (0.99-1.18)	1.09 (0.97-1.23)

IQR = 261.26 nW/cm²/sr

Model 1: adjusted for age at reference (continuous)

Model 2: further adjustment on reproductive and hormonal factors (parity, age at first full-term pregnancy, breastfeeding, oral contraceptive use, history of breast cancer among 1st-degree relatives, menopausal status at diagnosis, and menopausal hormonal therapy use), lifestyle-related factors at diagnosis (BMI, smoking and alcohol consumption), and education

Model 3: Model 2 + further adjustment on air pollution (NO₂) or residential greenness (NDVI at 300m buffer)

4.6. Sensitivity analysis for the association between breast cancer risk and other metrics of outdoor LAN exposure

We conducted sensitivity analyses to assess the association between breast cancer risk and other metrics of exposure assessment. Table 17 demonstrates the risk estimates using outdoor LAN exposure at inclusion, cumulative average exposure, and exposure during 5 years and 10 years before diagnosis for every one IQR increase in the respective measure of exposure. Except for the exposure at inclusion, the ORs were significantly elevated across all models for all exposure metrics.

4.7. Sensitivity analysis for the association between breast cancer risk and outdoor LAN after excluding extreme values

The sensitivity analyses for the association between breast cancer risk and outdoor LAN after excluding extreme values of LAN can be found in Table 18. Extreme values (n=582) were assumed to result from possible instrumental error. The interquartile range (IQR) before removing outliers was 261.26 nW/cm²/sr, slightly decreasing to 227.34 nW/cm²/sr after their removal. Compared to the ORs from our main analysis (1.11, 95% CI: 1.04-1.18, Model 3a, Table 14), ORs per IQR increase slightly decreased after exclusion of outliers (OR: 1.08, 95% CI: 0.99-1.17, Model 3a, Table 18) In fully adjusted models (Model 4), the ORs remained significantly elevated across all the quartiles, with OR in Q4: 1.27 (95% CI: 1.06-1.53).

Table 17: Odds ratio and 95% confidence intervals for the sensitivity analyses of the association between outdoor LAN and breast cancer risk using different exposure metrics in the case-control study nested within the E3N-Generations cohort, 1990–2011.

Per IQR increase in LAN	Case	Control	Model 1	Model 2	Model 3a: Model 2+NO ₂	Model 3b: Model 2 + NDVI	Model 4: Model 2 + NO ₂ + NDVI
			OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
At inclusion ^a	5222	5222	1.10 (1.04-1.15)	1.06 (1.01-1.12)	1.05 (0.98-1.13)	1.06 (1.00-1.12)	1.05 (0.98-1.13)
Cumulative average ^b	5222	5222	1.12 (1.06-1.16)	1.09 (1.03-1.15)	1.09 (1.01-1.18)	1.10 (1.02-1.21)	1.11 (1.02-1.21)
Average during 5 years before diagnosis ^c	4591	4591	1.13 (1.06-1.19)	1.10 (1.03-1.17)	1.11 (1.02-1.20)	1.14 (1.04-1.25)	1.15 (1.05-1.26)
Average during 10 years of diagnosis ^d	3433	3438	1.12 (1.05-1.20)	1.09 (1.02-1.17)	1.10 (1.00-1.21)	1.13 (1.01-1.26)	1.12 (1.00-1.26)

a: IQR = 208.68 nW/cm²/sr, b: IQR = 235.28 nW/cm²/sr, c: IQR = 271.76 nW/cm²/sr, restricted to women with at least 5 years of LAN exposure, d: IQR = 279.05 nW/cm²/sr, restricted to women with at least 10 years of LAN exposure

Model 1: adjusted for age at diagnosis (continuous)

Model 2: further adjustment on reproductive and hormonal factors (parity, age at first full-term pregnancy, breastfeeding, oral contraceptive use, history of breast cancer among 1st-degree relatives, menopausal status at reference, and menopausal hormonal therapy use), lifestyle-related factors at reference (BMI, smoking and alcohol consumption), and education

Model 3: Model 2 + further adjustment on air pollution (NO₂ or PM_{2.5} or PM₁₀) or residential greenness (NDVI at 300m buffer)

Model 4: Model 3a+ further adjustment on residential greenness (NDVI at 300m buffer)

Table 18: Odds ratio and 95% confidence intervals for the association between outdoor LAN and risk of breast cancer, after removing outliers in the case-control study nested within the E3N-Generations cohort, 1990-2011.

Outdoor LAN (nW/cm ² /sr)	Cases, n (%)	Controls, n (%)	Model 1	Model 2	Model 3a: Model 2+NO ₂	Model 3b: Model 2 + NDVI	Model 4: Model 2 + NO ₂ + NDVI
			OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Q1 (0-27.1)	1128 (23.0)	1241 (25.0)	Ref	Ref	Ref	Ref	Ref
Q2 (27.2-98.4)	1263 (25.8)	1243 (25.0)	1.13 (1.01-1.27)	1.12 (1.00-1.27)	1.14 (1.01-1.28)	1.15 (1.01-1.30)	1.15 (1.02-1.31)
Q3 (98.5-254.4)	1223 (25.0)	1242 (25.0)	1.12 (0.99-1.26)	1.09 (0.96-1.23)	1.13 (0.99-1.28)	1.13(0.98-1.31)	1.15 (1.00-1.33)
Q4 (254.5-688.0)	1281 (26.2)	1241 (25.0)	1.20 (1.05-1.36)	1.14 (0.99-1.30)	1.23 (1.06-1.44)	1.21 (1.01-1.44)	1.27 (1.06-1.53)
Per IQR increase	4895	4967	1.06 (0.99-1.13)	1.03 (0.96-1.11)	1.08 (0.99-1.17)	1.04 (0.95-1.14)	1.08 (0.98-1.19)

IQR= 227.34 nW/cm²/sr based on the distribution of LAN among controls only

All estimates are from conditional logistic regression models adjusted in the following order:

Model 1: adjusted for age at diagnosis (continuous)

Model 2: further adjustment on reproductive and hormonal factors (parity, age at first full-term pregnancy, breastfeeding, oral contraceptive use, history of breast cancer among 1st-degree relatives, menopausal status at diagnosis, and menopausal hormonal therapy use), lifestyle-related factors at diagnosis (BMI, smoking and alcohol consumption), and education

Model 3: Model 2 + further adjustment on air pollution (NO₂) or residential greenness (NDVI at 300m buffer)

5. DISCUSSION

5.1. Summary of main findings

In this case-control study nested in the French nationwide E3N-Generations Cohort, we identified a potential association between outdoor exposure to LAN and breast cancer risk with stable estimates after adjusting for potential confounders, including air pollution and residential greenness. The effect estimates tended to be higher among post-menopausal women.

Overall, these results provide evidence that may support the circadian disruption hypothesis²⁴⁴ which suggests that nocturnal melatonin inhibition resulting from LAN-induced circadian disruption leads to a heightened risk of breast cancer. Melatonin serves as an endogenously produced oncostatic agent; its suppression exaggerates the progression of cancer development^{125,245}. The nocturnal suppression of melatonin has also been linked with increased estrogen production, interference with estrogen receptor function, effects on immune function, and effects on free radical biology^{244,246,247}. This result observed among non-night-shift-working women underscores that the risk extends beyond occupation exposure to LAN, affecting a broader population residing in areas with elevated environmental exposure to LAN.

5.2. Comparison with existing literature

This study is one of the few studies that provided some evidence of an association between breast cancer risk and outdoor LAN assessed using the DMSP satellite images while adjusting for significant environmental covariates, including air pollution and residential greenness. Three previous cohort studies^{200,203,204} and two case-control studies^{182,206} have also reported a minor and augmented risk of breast cancer for the highest exposure to outdoor LAN compared to the lowest, while other studies provided no evidence^{199,201,205}.

Among the studies reporting a positive association, our risk estimates are comparable to those from 'The California Teacher's Study'²⁰⁰ reporting a hazard ratio of 1.12 (95% CI: 1.00, 1.26) for women exposed to the highest levels of LAN compared to the lowest, using a very comparable sample size (cases ~ 5000) during a similar follow-up period. However, the

California Teacher's Study²⁰⁰ and other studies^{202–204,206} are still limited by their inability to consider the effect of other environmental exposures.

5.3. Role of environmental covariates

It is crucial in studies assessing outdoor LAN, such as ours, to consider other important environmental covariates like air pollution, noise pollution and greenness, as they occur simultaneously, especially in the urban environment. These environmental factors may confound the association as they correlate with LAN exposure in urban areas and are suspected to be related to breast cancer risk. Exposure to NO₂, a proxy for traffic-related air pollution, has previously been reported to be associated with the risk of breast cancer in our study population²³⁸ and others^{99,103}. In our study, we adjusted additionally for PM_{2.5} and PM₁₀, proxies for non-traffic-related air pollution. Conversely, residential greenness has been hypothesized to have a protective effect on breast cancer risk through several mechanisms such as promoting physical activity, enhancing mental health and social cohesion as well as providing a physical barrier against outdoor exposures to LAN, air pollution, and noise^{106,111}. A few studies have reported a protective effect of greenness on breast cancer risk^{107,108}. Our results of higher ORs among residents of urban areas with low greenness also suggest a possible protective effect of greenness against exposure to outdoor LAN. Moreover, our study found a suggestive protective effect of exposure to residential greenness independently on breast cancer risk (Annex 15).

Our study found a strong correlation between these exposures (Annex 16), suggesting that higher levels of air pollution or lower levels of greenness could occur concurrently with outdoor LAN exposures, possibly due to living in urban areas. However, this high correlation did not affect our estimates, as they remained elevated even after the adjustment for NO₂, PM_{2.5}, and PM₁₀ or residential greenness. Furthermore, the high correlation did not result in variance inflation in our models, where we adjusted for more than one environmental covariate (Annex 17). Acknowledging possible co-occurrence and confounding by these environmental exposures is thus crucial to evaluating the precise role of outdoor LAN exposure in breast cancer risk.

Some of our findings revealed elevated ORs among residents of rural areas, which contrasts with the typical expectation of lower risk in those areas. Given the generally lower levels of air

pollution and higher levels of residential greenness in rural areas, this observation is unexpected and may point toward the role of unmeasured covariates that were not accounted for in our study.

Assessing residential greenness through the use of NDVI does not differentiate between the types of green spaces, such as parks, gardens, agricultural areas, and forests, which may affect breast cancer risk differently. Furthermore, traffic-related noise pollution is another environmental exposure that is a possible risk factor for breast cancer^{103,105,248} and has a speculated correlation with the LAN but was unavailable in our study.

5.4. Higher LAN exposure and use of LED streetlights

In this study, we observed high levels of exposure ranging from 0-2021.6 nW/cm²/sr comparable to the exposure levels in the Sister study (0- 2776.52 nW/cm²/sr)²⁰¹. This occurrence of high levels of exposure in this study could be explained by a more significant proportion of women living in urban areas at the time of diagnosis (>70%). In addition, the transition of traditional street lights to energy-efficient light-emitting diode (LED) occurred during the early 2000s²⁴⁹ along with the installation of more lights in streets in the past few decades¹⁸⁶. LED lights also emit more light with a shorter wavelength (blue light ~480 nm), which is argued to be the most disruptive to the circadian rhythm^{182,245,250}. However, LED lights have been in use just since the early 2000s^{249,251}, and the comparisons with other types of street lights have shown that other sources including halogen lamps, fluorescent lights, and mercury vapor lights, also emit a considerable proportion of blue light, causing melatonin suppression^{252,253}. These similarities in the blue light emissions from various sources and the development of streetlights over past decades could explain the overall higher exposure to LAN and, thus, the positive association.

Our results provide an indication of possible higher risk among post-menopausal women, which is in line with findings from the NIH-AARP diet and health study²⁰². We did not find conclusive results for the association of LAN exposure according to the hormone receptor status of breast tumors, similar to existing literature that remains inconclusive with conflicting results for these subtypes^{199,200,202,204}.

5.5. Role of Indoor exposure and sleep habits and other circadian disruptors

Despite the high level of exposure observed in this study, the actual amount of LAN exposure that penetrates the indoor sleep environment from the exterior is crucial. We addressed it to a certain extent by adjusting for residential greenness, which may provide a physical barrier and mask outdoor exposure. However, the exposure arising from using electronic devices, indoor lighting, curtains/blinders, and sleep habits were only measured after 2011 in the E3N-Generations cohort and thus remained unavailable for analyses in our study. Some studies using self-reported indoor exposure measures have reported conflicting results for its association with breast cancer risk ^{158,207–209,212}. Only a few studies have assessed indoor and outdoor LAN exposures ^{182,200,201,207}. Garcia-Saenz et al. reported a noteworthy association between breast cancer risk and blue light while adjusting for indoor exposure and other confounding factors ¹⁸².

Conversely, the Sister Study found a null association between outdoor LAN exposure and breast cancer, even among those reporting indoor LAN exposure from outdoor sources ²⁰¹. Future investigations could benefit from objective measurements using sensors to assess indoor and outdoor LAN exposure, considering sleep habits involving curtains, blinds, sleep masks, or electronic device usage at night. Such precise measurements would allow the estimation of outdoor LAN intensity penetrating sleeping areas and facilitate a thorough assessment of the risks associated with each type of exposure.

In addition to the environmental and individual exposure to light at night, other elements such as sleep and meal schedules can also affect the circadian rhythm, potentially inhibiting nocturnal melatonin production. Ill-timed meals and irregular sleep cycles, whether occurring independently or in conjunction with light at night, can result in as well as contribute to circadian disruption ^{128,254}. Further studies assessing individual exposure to LAN along with these circadian disruptors could provide a detailed insight into the underlying mechanism.

5.6. Strengths and limitation

The main strengths of our study include a prospective design of the E3N-Generations cohort, a large sample size, and the adjustment of several potential confounders, such as air pollution and residential greenness. The cases and control selected from the same population with 1:1 matching minimized the selection bias by ensuring that the cases and controls were comparable. Additionally, this study achieved a complete case ascertainment, as all incident cases during the follow-up were included, which further reduced potential selection bias by ensuring the representation of the study population, thus supporting the internal validity of the findings²³².

Our study is one of the largest studies to study breast cancer risk associated with environmental exposure to LAN, providing adequate statistical power to detect modest to weak associations. In addition to the large sample size, consistent results from the sensitivity analyses add validity to our findings.

The E3N-Generations cohort comprised females involved in teaching-related professions with standard work schedules; thus, the confounding from night shift work exposure is highly unlikely. This excluded the possibility of confounding due to night shift work exposure. Residual confounding has been reduced to a certain extent by adjusting for multiple possible confounders, air pollution, and residential greenness. However, the residual confounding due to other unmeasured environmental and individual-level LAN exposure could not be ruled out.

In our analyses, we used the assessment of LAN exposure at the time of diagnosis, which does not capture the etiologically necessary time for breast carcinogenesis and does not account for the changes in exposure with changes in residential addresses. However, its high correlation with other exposure metrics covering up to 10 years before diagnosis made it the most appropriate metric for the primary analysis as a proxy for the total exposure. This choice benefitted our analysis by maintaining homogeneity in the exposure metric and preventing loss of sample size. Even though the information on LAN exposure over an extended period before diagnosis (beyond 1990) was not available for all women in our study, we conducted sensitivity analyses in the subsets of women based on exposure information during the 5 years or 10 years before diagnosis and observed similar results.

Assessing outdoor LAN using DMSP images has been criticized for its low resolution, potential exposure saturation in urban areas, and non-differentiation between the spectral wavelengths¹⁸¹, which persist in our exposure assessment methods. These underscore the need for further investigations with advanced LAN assessment using ISS images used by the MCC-Spain study¹⁸² that provide higher resolution (30 m) compared to DMSP (650 m). The DMSP images are criticized for their inability to provide variability in urban areas where the exposure is usually higher. Our sensitivity analyses of removing extremely high LAN values (assumed to be caused by the instrumental error), showed consistent results. In addition, we used radiance-calibrated high-dynamic images, which provided adequate variability in the exposure in urban areas²¹⁹ and addressed the limitation to a certain extent. For this study period (1990-2011), the ISS Images were unavailable; thus, DMSP remained the only source of satellite images available. Further studies should also carefully explore the association using ISS images, considering possible confounding due to different urban exposures, objectively measured indoor and individual-level exposures, and other circadian disruptors.

5.7. Conclusion

Overall, in this nested case-control study in a prospective cohort, we identified a potential association between breast cancer risk and outdoor LAN exposure assessed using satellite images, adjusting for potential confounders like air pollution and residential greenness. Our findings may lend credence to the hypothesis that LAN-induced circadian disruption and melatonin inhibition lead to augmented risk for hormone-dependent cancer like breast cancer and that this risk may extend beyond occupational exposure among night shift workers. Further population-based studies with a more precise assessment of indoor and outdoor LAN are warranted, and factoring in other circadian disruptors like sleep and meal schedule along with other urban exposures are warranted to assess in-detail the interplay of environmental and individual exposures in breast cancer risk.

**CHAPTER 4: NIGHT SHIFT WORK AND BREAST CANCER RISK IN THE
CONSTANCES COHORT**

1. STUDY OBJECTIVES

In this chapter, we shift the focus to examining the role of circadian disruption due to night shift work and its association with breast cancer risk, analyzed using the data from C3-Nuit study nested in the CONSTANCES cohort. This chapter aims to assess the impact of various features of night shift work on breast cancer risk. This chapter will outline the comprehensive methods for assessing night shift work exposure, analyzing these data, and interpreting the results.

2. MATERIALS AND METHODS

The C3-Nuit study, which will serve as the study population in this thesis, is a case-control study nested in the CONSTANCES Cohort (*Cohorte des consultants des Centres d'examens de santé*), a comprehensive population-based cohort in France. The CONSTANCES cohort will first be described before focusing on the C3-Nuit study.

2.1. The CONSTANCES cohort

The CONSTANCES cohort was designed to serve as a robust epidemiological research infrastructure focusing on occupational and social factors, chronic diseases, and aging²⁵⁵. The cohort was established in collaboration with National Health Insurance Fund administered by the *Caisse nationale d'assurance maladie des travailleurs salariés* (CNAMTS) and with the *Caisse nationale d'assurance vieillesse* (CNAV)²⁵⁵. The primary objective of CONSTANCES is to facilitate research on diverse health issues, focusing on the occupational and social determinants of health and the aging process. The cohort integrates multiple data sources, exploring various health outcomes and determinants.

2.1.1. Study participants

Participants in the CONSTANCES cohort were randomly selected among 18–69 years French adults insured by the National Health Insurance Fund, which covers approximately 85% of the population. Subjects were invited to visit a "*Centre d'Examen de Santé*" (CES) for a comprehensive health examination and to complete a detailed questionnaire. The CES were distributed all across Metropolitan France (Fig 18). The participating CES are located in 20

different departments. Since the beginning of enrollment in 2012, the cohort successfully enrolled 202,045 subjects by February 2020 ²⁵⁶.

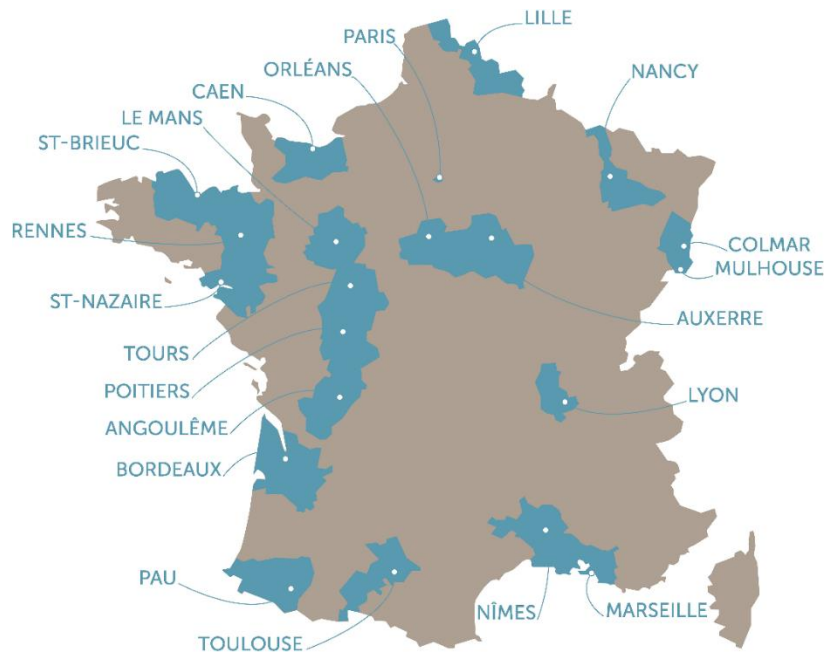


Figure 18: Location of the 24 participating Health Prevention Centers (CES, Centre d'examens de santé) throughout the 21 cities in metropolitan France ²⁵⁶.

2.1.2. Data collection in CONSTANCES cohort

At inclusion and during follow-up, data is collected actively or passively.

Active data collection is done through self-administered questionnaires at inclusion and during annual follow-up. Follow-up questionnaires are sent annually in paper or online, according to the participant's choice. Information on lifestyle and health, women's health, job history, occupational exposure, medical history, etc., are collected through the questionnaire. At inclusion in the cohort, participants were invited to one of 24 CES for a comprehensive health examination, biometric measurements, blood pressure assessment, electrocardiogram, and blood and urine analyses. A comprehensive clinical examination is conducted at inclusion and every four years during follow-up.

Passive data collection is done by linkage to national administrative databases: CNAV (*Caisse Nationale d'Assurance Vieillesse*) and SNDS (*Système National des Données de Santé*). The

CNAV provides vital information on socio-professional status from first employment or social benefit until retirement, including the type of job and contract, salary, and periods of activity/non-activity of individuals (unemployment, absence due to illness, maternity leave, etc.). The participants from the CONSTANCES cohort are regularly searched in the SNDS database using a unique personal identifier to provide medico-administrative data such as consultations or hospitalizations, including diagnoses, prescribed drugs, and reimbursement claims.

Thus, passive data collection provides a wide range of information on social and demographic characteristics, socio-economic status, life events, occupational factors, reported prevalent and incident diseases, long-term chronic diseases and hospitalizations, sick leaves, disabilities and injuries, healthcare utilization and services provided, and causes of death if applicable. The national databases are updated regularly, which ensures detailed longitudinal follow-up with minimal loss to follow-up.

2.1.3. Data available from the CONSTANCES cohort

A large data set is collected for all participants during CES visits through physical examinations, using self-administered questionnaires at inclusion and during annual follow-ups.

Socio-demographic characteristics

Information on date of birth, employment status, level of education, income level, marital status, household composition, socio-economic status of parents and spouse, living conditions, and geographic origin of the participants and their parents were collected.

Medical, reproductive, and lifestyle-related characteristics

The CONSTANCES cohort collected information on the personal and family medical history, including any health condition, hospitalization, chronic conditions, disabilities, absence from work, date, and the medical cause of death (if applicable). Information on reproductive and hormonal factors, including age at menarche and menopause, oral contraceptive use, menopausal hormonal therapy (MHT) use, history of gynecological diseases and surgeries (hysterectomy, oophorectomy), outcomes of each pregnancy, duration of breastfeeding and infertility treatment were also collected.

The physical examination in CES collected information on biometric measurements, including weight, height, waist and hip circumference, and blood pressure readings, as well as on electrocardiograms, vision and hearing tests, and spirometry to assess lung function. Blood and urine analyses were also performed during the regular visits. For participants aged 45 and older, additional assessments for functional, physical, and cognitive capacities were also performed during the follow-up visits.

Lifestyle-related information on dietary habits, physical activity levels, smoking, and alcohol consumption were collected.

Occupational and environmental factors

Information on occupational history, occupational exposure to chemical, physical, and biological agents, ergonomic factors, work-related stress, and environmental exposures were collected.

2.2. The nested case-control study: C3-Nuit

The C3-Nuit study (*Cancers dans la Cohorte Constances et Travail de nuit*) was primarily designed to investigate the role of night shift work, sleep, and meal schedules in the risk of breast, prostate, and colorectal cancers. Since the detailed information on these factors was not collected comprehensively in the CONSTANCES database, a C3Nuit-specific questionnaire was developed and administered to a subset of CONSTANCES participants using a nested case-control study design.

2.2.1. Selection of cases and controls in the C3-Nuit study

Case's selection

All participants of the CONSTANCES cohort identified with a new diagnosis of cancer of the breast, prostate, or colorectum between the date of enrollment in the cohort and Dec. 31, 2020, were eligible for inclusion in C3-Nuit. Incident cases were identified from two sources:

- Annual questionnaire: In the questionnaire sent annually to all cohort participants, participants were asked to indicate any health condition they suffered in the last 12 months, where they could self-report if they had any cancer and specify its site.
- The SNDS database: From the SNDS database, the cancer cases among CONSTANCES participants were identified from the diagnoses of cancer coded according to the

ICD10th revision (ICD10 C50.919 for breast cancers), as well as from specific algorithms using the information on treatment and medical examinations for the cancers of interest.

The identified cancer cases are further confirmed by a dedicated CONSTANCES platform using medical records.

Control's selection

Controls were frequency-matched to the cases by age and sex using an incidence density sampling procedure²⁵⁷. They were selected at random among cohort participants of the same age and sex, enrolled in CONSTANCES, and free of cancer at the time of diagnosis of the cancer cases. Male and female controls were frequency-matched to cases of prostate and breast cancer, respectively. This same set of controls will be used for colorectal cancer. The pool of eligible controls was stratified by sex and age into predefined five-year age groups. Eligible controls were first contacted via telephone, and those who refused consent were excluded. For this thesis, only breast cancer cases and female controls will be considered.

The "reference year" was defined as the year of diagnosis for the cases and the year of selection for the matched controls. Only information on risk factors before this date was considered in the analysis.

2.2.2. Data collection in C3-Nuit study

The C3-Nuit questionnaire

A specific questionnaire was developed for C3Nuit to obtain detailed information on night shift work, sleep patterns, and meal schedules. Trained interviewers administered the questionnaire during a telephone call using Computer Assisted Personal Interviews (CAPI). Between July 2019 and Jan 2023, women were interviewed by trained investigators with a detailed Computer Assisted Personal Interviews (CAPI). The interviews lasted between 10 to 65 minutes. The questionnaire can be found in Annex 18.

The questionnaire included details on the employment history, including the start and end year of each job, the profession, and the sector of activity, indicating if they worked full-time

or part-time at each job. All jobs held until the date of enrollment in the CONSTANCES cohort were pre-coded according to the PCS (*Professions et Catégories Socioprofessionnelles*)²¹⁵ and NAF (*Nomenclature des Activités Françaises*) codes²⁵⁸. Additional information on career history was collected and supplemented during the telephone interview to update the occupational changes during follow-up.

The questionnaire elicited information on work schedules for each job for at least 6 months, held during work history. Subjects were asked if the work schedule of a given job was fixed, rotating, or irregular from one day to another, allowing the classification of each job into exclusive categories of "fixed," "alternating," and "irregular." Information on work time schedules specific to each job type was obtained to allow identification of jobs that included night shifts (see below section 1.3.1).

The questionnaire also collected information on sleep and meal schedules for work and rest days. Information on chronotype, ideal sleep hours, naps during the day on work days or work-off days, time of going to bed, time required to fall asleep, etc., were also collected. Regarding the meal schedules, the time and duration of each meal, snacking between the meals, and frequency of snacking during work and rest days were collected. Apart from the chronotype, these data were not used in the present thesis. Chronotype is the individual trait that defines one's circadian phase and inclination for either morning or evening type¹¹⁷. In the questionnaire, self-reported chronotype information was gathered as either morning, evening, or neutral chronotypes.

2.3. Conceptualization of night shift work variable

2.3.1. Night shift work definition

The present analysis defined night work as "*working for at least 3 hours between midnight and 5 am*".

Individuals who reported working night shifts according to this definition in any job for at least 6 months during their entire professional history were considered as ever-night shift workers. Depending on the schedules of the jobs, individuals were categorized as:

Fixed night shift workers: individuals having worked night shifts with little (+/-1h) to no variations of the work schedule from day to day or from week to week.

Alternating night shift workers: individuals having worked night shifts with a changing schedule that follows a regular rhythm, i.e., rotating every day, week, or month.

Irregular night shift workers: individuals working night shifts without any fixed or alternating schedule.

2.3.2. Night shift work exposure metrics

Further, for each type of night shift work, the following aspects of night shift work were also assessed:

Frequency of night shift work: The number of nights worked per week, calculated as the mean frequency of night shifts, weighed on the duration of each night work period. Details on calculating average frequencies for alternating and irregular night shift work can be found in Annex 19.

Duration of night shift work: Calculated in years, using the year of starting and quitting the night shift work.

Length of every shift: Calculated in hours, using the start and end times of shifts for all types of night shift work. The mean length of the night shift was calculated as the mean of the lengths of shifts weighed on the duration of each night work period.

Cumulative number of nights: Total number of nights worked during the professional career, calculated as a product of average frequency and the duration of night shift work for all types.

The following equation was used to calculate the cumulative exposure:

*Total nights: frequency (nights/week) * duration (years) *52*

Time since quitting last night shift work: To examine the effects of time patterns of exposure to night work, we also analyzed the association of breast cancer risk with the time since last night shift work, i.e., during 5, 10, and 20 years preceding the reference year. It was calculated based on the year of quitting night shift work and was calculated as the difference between the year of stopping night shift work and the year of reference.

Consecutive Night Shifts (Unique to Alternating Night Shift Work): Uniquely for alternating night shift work, the number of consecutive nights worked was also analyzed. This metric was categorized into <3 nights, 3-4 nights, and >4 nights.

3. ANALYTICAL STRATEGY

To assess the association between exposure to night shift work and breast cancer risk, a series of statistical methods were applied. Initially, descriptive statistics were used to characterize the study population and to explore the distribution of night shift work among the study population. Following this, regression models were applied to obtain the risk estimates for this association while also assuring the robustness of the models.

3.1. Participants included in the analysis

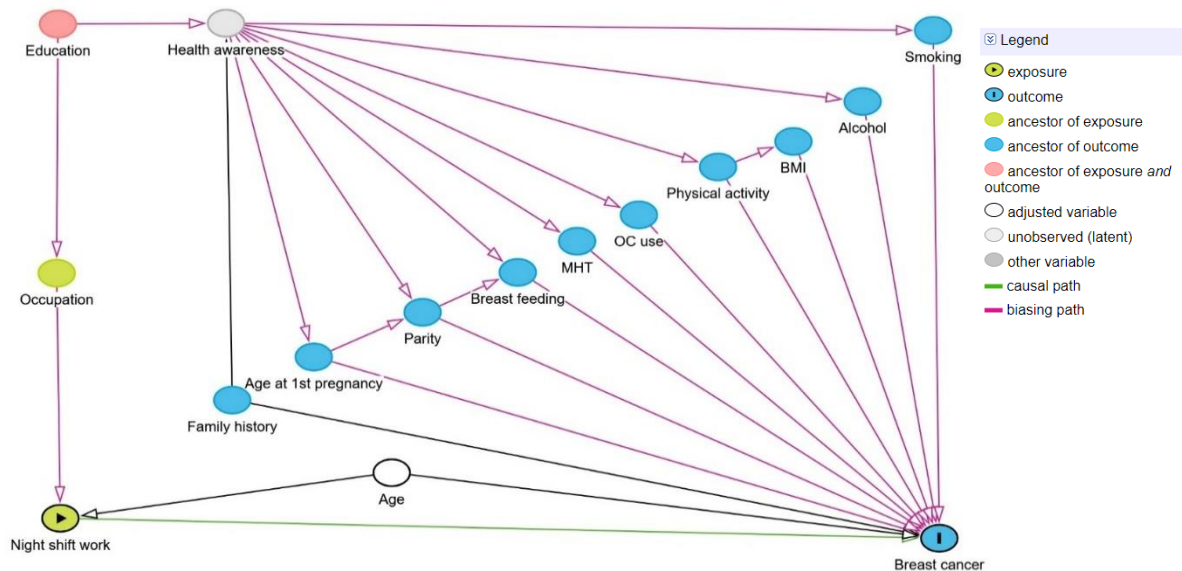
Out of 1698 (674 cases and 1024 controls) women, 8 controls and 3 cases with missing information on job history and several other covariates were excluded, leaving 1687 women (671 cases and 1016 controls) for the main analysis.

3.2. Choice of covariates

The variables to be considered as potential confounders and included in the main analyses were selected using the Directed Acyclic Graph (DAG) approach ²⁵⁹. Potential covariates considered in this study are shown in Fig 19, which included age at reference, age at first full-term pregnancy, parity, menopausal status, oral contraceptive use, MHT use, family history of breast cancer in first-degree relatives, alcohol consumption, smoking, body mass index (BMI), physical activity, educational level (a proxy for SES). Age, being the matching factor, was forced into the DAG. The causal links between the covariates, night shift work, and breast cancer were

drawn based on a priori information from available literature. DAG was drawn using the DAGitty software ²²¹.

Figure 19: Directed Acyclic Graph (DAG) for the association between night shift work and breast cancer risk cancer in the C3-Nuit study nested within the CONSTANCES Cohort.



BMI: Body-mass Index, MHT: Menopausal hormonal therapy, OC: Oral contraceptives.

The minimal adjustment set identified from the DAG was:

“Age, Age at 1st pregnancy, Alcohol, Breastfeeding, Family history of BC, MHT, OC use, Parity, Physical activity, Smoking”

The set identified included a wide range of breast cancer risk factors that were adequately measured and adjusted for in the main analyses.

3.2.1. Definition of covariates included in the analysis

Age

Age at reference date was calculated using the date of birth for all participants, the date of diagnosis for cases, and the date of interview for controls. Age was adjusted for in all models as a continuous variable.

Education level

Information on the highest education level attained was collected through the self-administered questionnaires and was categorized into four levels in the analysis: primary school or lower, basic secondary school, and university education.

Family history of breast cancer

Information on cancer history in mothers was used as a binary variable (yes, no) in the models.

Parity

Parity, defined as the number of full-term pregnancies, was determined using pregnancy information collected at inclusion. Parity was used as a categorical variable in the models with 4 categories: nulliparous, 1, 2, and ≥ 3 full-term pregnancies.

Age at first full-term pregnancy

The age at first full-term pregnancy only for parous women variable was categorized into four categories: <22, 22-24, 25-27, and >27 years.

Oral contraceptives

Oral contraceptive use was categorized as a binary variable: ever, never.

Menopausal status and menopausal hormonal therapy use

Menopausal status was determined using a combination of hormonal and reproductive factors. Women were categorized as pre-menopausal if they were still menstruating at inclusion, had menstruated within the last 12 months, were on oral contraceptives that halted menstruation, were not menstruating due to breastfeeding, or had not had a total bilateral oophorectomy. Conversely, women were considered post-menopausal if their last menstrual period occurred more than 12 months before the inclusion date, they had undergone a total bilateral oophorectomy, or they were using MHT. For women whose last menstrual period was unknown, menopausal status was determined based on age: those under 50 at inclusion were classified as pre-menopausal, while those 50 and older were classified as post-menopausal.

MHT included estrogen-only or estrogen-progesterone treatments among post-menopausal women. In the models, a combined variable of menopausal status and MHT was used with three modalities: pre-menopausal women, post-menopausal women with MHT use, post-

menopausal without MHT use, and post-menopausal women with missing information on MHT.

Body mass index

BMI at the inclusion date was calculated from height and weight information gathered during the in-person interview. The WHO's BMI classification was used to create the BMI variable: <18.5, 18.5-24.9, 25-29.9, and ≥ 30 kg/m².

Physical activity

Physical activity was calculated using two variables: physical activity at work and outside work based on the last job held at the time of inclusion.

Physical activity at work was categorized into five levels: 1: sedentary or never worked, 2: light work equivalent to lifting less than 10 kg, 3: medium weighted work equivalent to lifting 10-25 kg, 4: heavy work equivalent to lifting more than 25 kg.

Physical activity outside work was assessed as scored from 0 to 6, 0 meaning sedentary and 6 meaning very active. This variable was recategorized into 5 categories: 1: score 0 indicating sedentary, 2: scores 1-2 indicating slightly active, 3: scores 3-4 medium active, and 4: scores 5-6 indicating very active.

The scores from these two variables were summed for each woman to create a composite score for total physical activity within and outside of work, with the following levels:

Scores 0-2: Sedentary

Scores 3-4: Lightly active

Scores 5-6: Moderately active

Scores 7-8: Highly active

Thus, in the analysis, physical activity was used as a categorical variable with four modalities: sedentary, lightly active, moderately active, and highly active.

Tobacco consumption

Tobacco smoking at inclusion was used as a categorical variable with 3 categories: non-smokers, former smokers, and current smokers.

Alcohol consumption

Alcohol consumption in the last 12 months before inclusion was assessed using the Alcohol Use Disorders Identification Test (AUDIT) score, with scores ranging from 0 to 35²⁶⁰. AUDIT scores were categorized as follows

Scores 0-7: Low risk of alcohol use disorder

Scores 8-15: Increasing risk of alcohol use disorder

Scores 16-19: Higher risk of alcohol use disorder

Scores ≥ 20 : Alcohol dependence

In our analysis, alcohol use was categorized into non-drinkers, moderate drinkers (score 0-7), and heavy drinkers (score ≥ 8).

3.3. Statistical methods

A descriptive comparison was made between cases and controls for their socio-demographic, reproductive, hormonal, and lifestyle-related characteristics using chi-square tests for categorical variables and Wilcoxon signed-rank tests for continuous variables, with a statistical significance level set at $p=0.05$. Multivariable unconditional logistic regression models were applied to calculate the odds ratios (ORs) and the corresponding 95% confidence intervals (CIs) for the main analyses of the association between night shift work and breast cancer risk.

Following exposure metrics for night shift work were used in the main analyses for all types of night shift work combined and separately:

- Ever/never, all types combined, and specific types
- Duration of night shift work (years) in categories: ≤ 1 , $> 1 < 10$ y, $\geq 10 < 20$, $\geq 20 < 30$, and ≥ 30 years
- Frequency of night shift work (nights/week) in categories: < 1.0 , $\geq 1.0 < 2.0$, $\geq 2.0 < 3.0$, and ≥ 3.0 nights per week
- Length of night shifts (hours/shift) in categories: < 10 , $\geq 10 < 13$, and ≥ 13 hours per shift
- Cumulative nights worked in quartiles based on the distribution among controls
- Time since quitting last night shift work in categories: ≤ 5 , $> 5 < 20$, and ≥ 20 years
- Consecutive nights worked for alternating night shift work in categories: < 3 , $\geq 3 \leq 4$, and > 4 nights

Several logistic regression models were employed with potential confounders adjusted progressively from Model 1 to Model 3.

Model 1: Adjusted age at diagnosis in continuous form.

Model 2: Further adjusted for reproductive factors, including age at first full-term pregnancy, parity, oral contraceptive use, menopausal status and MHT use, breastfeeding, and lifestyle-related factors, which included alcohol consumption, tobacco smoking, and physical activity.

Model 3: Further adjusted for education used as a proxy for socio-economic status.

Additional analyses explored the modification of the association between night shift work and breast cancer by menopausal status and chronotypes based on fully adjusted models (Model 4). We further investigated the impact of latency of exposure by categorizing the night shift work exposure based on whether they commenced before or after the first pregnancy.

3.3.1. Sensitivity analysis

Sensitivity analyses were conducted, excluding irregular night shift work, to address the potential misclassification of irregular jobs as night shift work.

We also estimated the minimum detectable ORs for this study. Estimations of the minimum detectable OR in the C3-Nuit study can be found in Annex 4.

All statistical analyses were conducted using SAS software version 9.4 (Cary, North Carolina).

4. RESULTS

4.1. Participants included in the study

A total of 1200 eligible breast cancer cases were identified and validated between May 2019 and May 2022. Of these, 276 refused to participate, 219 could not be contacted, and 31 died before the interview. Consequently, only 674 breast cancer cases were included in the study, resulting in a participation rate of 56%. A total of 1,590 female controls were identified. Of these, 248 did not consent, 307 could not be contacted, and 1 died before the interview. Therefore, only 1,024 controls were included in the study, with a participation rate of 64%. The study participants thus comprised of 1687 women, 671 cases (39.8%), and 1016 controls (60.2%).

The participation rate among cases and controls was notably low. A detailed comparison of participating and non-participating women by their case-control status is provided in Table 19. A comparison of participating and non-participating women in the C3-Nuit study revealed that participating women were more likely to have higher educational attainment than non-participating women. Participants and non-participating women were comparable in socio-demographic, lifestyle-related, and reproductive characteristics.

Table 19: Comparison of participating and non-participating women in the C3-Nuit study nested within the CONSTANCES Cohort, 2012-2020.

	Participants in C3-Nuit			Non-participants in C3-Nuit		
	Cases	Controls	p-value	Cases	Controls	p-value [†]
Socio-demographic characteristics						
Age at reference, n (%)						
<50 years	182 (27)	269 (27)	0.92	160 (30)	132 (23)	0.06
50-59 years	187 (28)	273 (27)		132 (25)	145 (26)	
60-69 years	233 (35)	363 (36)		175 (33)	207 (36)	
≥70 years	69 (10)	111 (11)		64 (12)	84 (15)	
Socio-professional categories, n (%)						
Farmers/spouses of farmers	1 (0)	-	0.34	-	-	0.36
Auto-entrepreneur	5 (1)	14 (1)		9 (2)	14 (3)	
Managers/high-level jobs	186 (29)	251 (26)		88 (18)	102 (19)	
Intermediary jobs (teachers/professors)	214 (34)	353 (36)		160 (32)	137 (26)	
White collar jobs	196 (31)	284 (29)		183 (37)	209 (40)	
Blue collar jobs	13 (2)	31 (3)		31 (6)	28 (5)	
Never worked	1 (0)	5 (1)		5 (1)	9 (2)	
Missing	23 (4)	32 (3)		20 (4)	29 (6)	
Education, n (%)						
No education	10 (2)	22 (2)	0.59	23 (5)	37 (7)	0.005
CFG/ BEPC	46 (7)	75 (8)		45 (9)	81 (15)	
CAP/BEP	93 (14)	147 (15)		93 (18)	114 (21)	
Baccalauréat ou diplôme équivalent	95 (14)	165 (17)		98 (19)	72 (13)	
Bac + 2 ou + 3	196 (30)	271 (27)		131 (26)	128 (24)	
Bac + 4	85 (13)	117 (12)		54 (11)	40 (7)	
Bac + 5 or more	138 (21)	202 (20)		67 (13)	71 (13)	
Missing	8	17		20	25	
Marital status, n (%)						
Single	109 (16)	172 (17)	0.35	82 (16)	93 (17)	0.96
Co-habitation	440 (66)	654 (66)		310 (61)	324 (59)	
Separated/Divorced	115 (17)	168 (17)		120 (23)	129 (24)	
	7	22		19	22	
Lifestyle-related and personal characteristics						
BMI, n (%)						
Underweight	15 (2)	35 (4)	0.50	17 (3)	17 (3)	0.98
Normal	374 (57)	586 (59)		283 (54)	296 (53)	
Overweight	187 (28)	262 (26)		148 (28)	160 (29)	
Obese	84 (13)	119 (12)		73 (14)	82 (15)	
Missing	11	14		10	13	

	Participants in C3-Nuit			Non-participants in C3-Nuit		
	Cases	Controls	p-value	Cases	Controls	p-value†
Physical activity outside work, n (%)						
No activity or sedentary	56 (9)	69 (7)	0.06	44 (9)	41 (8)	0.54
Low activity	110 (17)	119 (12)		79 (16)	82 (16)	
Slightly active	118 (18)	179 (19)		104 (21)	109 (21)	
Active	162 (25)	264 (28)		133 (27)	131 (25)	
Moderately active	101 (16)	187 (20)		78 (16)	77 (15)	
Highly active	94 (15)	143 (15)		51 (10)	76 (15)	
Missing	30	55		42	52	
Physical activity at work, n (%)						
Sedentary work	382 (59)	479 (50)	0.002	238 (47)	240 (46)	0.31
Light work ~10 kg	189 (29)	338 (35)		180 (36)	177 (34)	
Medium weight work ~10-25 kg	59 (9)	104 (11)		65 (13)	83 (16)	
Heavy work ~ >25 kg	19 (3)	34 (4)		14 (3)	14 (3)	
Never worked	3 (1)	4 (0)		5 (1)	11 (2)	
Missing	19	57		29	43	
Tobacco smoking, n (%)						
Non-smoker	316 (48)	546 (56)	<.0001	223 (46)	279 (53)	0.07
Current smoker	119 (18)	130 (13)		83 (17)	90 (17)	
Former smoker	224 (34)	294 (30)		180 (37)	157 (30)	
Missing	12	46		45	42	
Alcohol consumption using AUDIT score, n (%)						
Abstinent	44 (4)	19 (3)	0.11	45 (8)	46 (9)	0.09
Neither abusive nor dependent	776 (77)	512 (76)		389 (70)	351 (67)	
Dependent	16 (2)	15 (2)		12 (2)	14 (3)	
Abusive	100 (10)	84 (13)		57 (10)	78 (15)	
Score missing	74 (7)	40 (6)		56 (10)	38 (7)	
Missing	1	6		4	9	
Personal history of cancer, n (%)						
No	43 (7)	8 (1)	<.0001	37 (7)	11 (2)	0.00
Yes	619 (94)	973 (99)		467 (93)	533 (98)	
Missing	9	35		27	24	
Maternal history of cancer, n (%)						
No	468 (70)	773 (78)	0.05	367 (72)	430 (78)	0.05
Yes	198 (30)	221 (22)		146 (29)	123 (22)	
Missing	5	22		18	15	
Reproductive and hormonal characteristics						
Age at menarche, n (%)						
<12 year	148 (23)	164 (18)	0.001	89 (19)	85 (17)	0.24
12 year	148 (23)	202 (22)		113 (24)	137 (27)	

	Participants in C3-Nuit			Non-participants in C3-Nuit		
	Cases	Controls	p-value	Cases	Controls	p-value [†]
13 year	153 (24)	210 (23)		124 (26)	108 (22)	
14 year	89 (14)	187 (20)		74 (15)	91 (18)	
≥15 year	95 (15)	165 (18)		80 (17)	80 (16)	
Missing	38	88		49	67	
Parity, n (%)						
Nulliparous	86 (14)	147 (16)	0.38	83 (17)	88 (17)	0.45
1 child	107 (17)	143 (15)		101 (21)	91 (18)	
2 children	274 (43)	400 (43)		189 (39)	199 (39)	
≥ 3 children	166 (26)	249 (27)		116 (24)	133 (26)	
Missing	38	77		40	57	
Menopausal status, n (%)						
Pre-menopausal	296 (44)	420 (41)	0.25	242 (46)	217 (38)	0.01
Post-menopausal	375 (56)	596 (59)		287 (54)	351 (62)	

†: p-values derived from chi-square test for categorical variables

4.2. Descriptive characteristics

Table 20 compares the selected socio-demographic, personal, lifestyle-related, reproductive, and hormonal characteristics between cases and controls.

4.2.1. Socio-demographic, personal, lifestyle-related characteristics

Cases and controls had similar ages at reference. The distribution of cases and controls was similar across occupation categories, educational attainment, marital status, BMI, and physical activity. Cases were more likely to be current or former smokers than controls (51.1% vs. 41.5%) and had a higher tendency to be heavy drinkers of alcohol than the controls (17.8% vs 11.8%). The history of maternal breast cancer was found to be notably higher among cases (16.4%) than in controls (7.3%).

4.2.2. Reproductive and hormonal characteristics

Most of the reproductive and hormonal characteristics of cases and controls were comparable. However, the cases had an earlier average age at menarche (12.8 years) than the controls (13.1 years). Besides, parity, age at first pregnancy, breastfeeding, and the use of oral contraceptives were found to be similar among cases and controls. Among post-menopausal women, the use of menopausal hormonal therapy was found to be more prevalent among cases than controls (14.7% vs 8.6%) at inclusion.

4.2.3. Chronotype

In our study, more cases than controls (52.1% vs. 48.7%) were likely to have morning chronotype, while more controls than cases (21.2% vs. 17.3%) were neutral.

Odds ratios and their corresponding 95% confidence intervals for the association of these variables with the breast cancer risk independent of the exposure in this study can be found in Annex 20.

Table 20: Descriptive characteristics of women in the C3-Nuit study nested within the CONSTANCES Cohort, 2012-2020.

	Total (N = 1687)	Cases (n = 671)	Controls (n = 1016)	p-values†
Socio-demographic/ personal lifestyle-related characteristics				
Age at reference				
Mean ± SD	56.8 ± 10.4	56.8 ± 10.2	56.7 ± 10.5	0.67
Occupation, n(%)				
Blue-collar jobs/ Farmers	45	14 (2.1)	31 (3.1)	0.37
Intermediary jobs	586	219 (32.6)	367 (36.1)	
Managers/white-collar jobs	917	382 (56.9)	535 (52.7)	
Never worked /others	61	24 (3.6)	37 (3.6)	
Missing	78	32 (4.8)	46 (4.5)	
Education, n(%)				
Primary education or lower	153	56 (8.4)	97 (9.6)	0.45
Secondary education	500	188 (28.0)	312 (30.7)	
Undergraduate degree	492	204 (30.4)	288 (28.4)	
University degree	542	223 (33.2)	319 (31.4)	
Marital Status, n(%)				
Single	281	109 (16.4)	172 (17.3)	0.42
Married or cohabitating	1094	440 (65.6)	654 (64.4)	
Separated/ Divorced/ Widowed	283	115 (17.3)	168 (16.9)	
Missing	29	7 (1.0)	22 (2.2)	
BMI (kg/m²), n(%)				
<18.5	50	15 (2.2)	35 (3.4)	0.37
18.5-4.9	960	374 (55.7)	586 (57.5)	
25-29.9	449	187 (27.9)	262 (25.8)	
≥30	203	84 (12.5)	119 (11.7)	
Missing	25	11 (1.6)	17 (1.4)	
BMI among pre-menopausal women				
<18.5	24	8 (3.0)	16 (4.2)	0.36
18.5-4.9	427	180 (67.2)	247 (65.0)	
25-29.9	138	61 (22.8)	77 (20.3)	
≥30	59	19 (7.1)	40 (10.5)	
BMI among post-menopausal women				
<18.5	26	7 (1.7)	19 (3.0)	0.15
18.5-4.9	558	205 (50.9)	353 (55.5)	
25-29.9	311	126 (31.3)	185 (29.1)	
≥30	144	65 (16.1)	79 (12.4)	
Missing				
Physical activity, n(%)				
Sedentary or low physical activity	19	7 (1.0)	12 (1.2)	0.19
Moderately active	998	417 (62.2)	581 (57.2)	
Active	605	226 (33.7)	379 (37.3)	
Highly active	65	21 (3.1)	44 (4.3)	

	Total (N = 1687)	Cases (n = 671)	Controls (n = 1016)	p-values†
Tobacco smoking, n(%)				
Non-smokers	862	316 (47.1)	546 (53.7)	0.002
Current smokers	249	119 (17.7)	130 (12.7)	
Former smokers	518	224 (33.4)	294 (28.8)	
Missing	58	12 (1.8)	46 (4.5)	
Recent alcohol consumption, n(%)				
Never drinkers	63	19 (2.8)	44 (4.3)	0.05
Moderate drinkers	1288	512 (76.3)	776 (76.4)	
Heavy drinkers	215	99 (17.8)	116 (11.4)	
Missing	121	41 (6.1)	80 (7.9)	
History of maternal breast cancer, n(%)				
Yes	184	110 (16.4)	74 (7.3)	<0.0001
No	1476	556 (82.9)	920 (90.5)	
Missing	27	5 (0.7)	25 (2.2)	
Reproductive and Hormonal characteristics				
Age at menarche				
Mean ± SD	12.9 ± 1.7	12.8 ± 1.7	13.1 ± 1.6	0.0002
Age at menarche, n(%)				
<12 years	438	186 (27.7)	252 (24.8)	0.007
12-14 years	713	301 (44.9)	412 (40.5)	
≥14 years	536	184 (27.4)	352 (34.7)	
Parity, n(%)				
Nulliparous	233	86 (12.8)	148 (14.5)	0.28
1-2 children	924	381 (56.8)	543 (53.4)	
≥3 children	415	166 (24.7)	249 (24.5)	
Missing	115	38 (5.7)	77 (7.6)	
Age at 1st First pregnancy ^a				
Mean ± SD	27.2 ± 4.8	27.4 ± 4.8	27.0 ± 4.8	0.69
Age at 1st First pregnancy ^a				
<30 years	977	394 (72.0)	583 (73.6)	
≥30 years	362	153 (28.0)	209 (26.4)	
Breastfeeding, n(%)^a				
Yes	899	363 (66.4)	536 (67.7)	0.61
No	401	168 (30.7)	233 (29.4)	
Missing	39	16 (2.9)	23 (2.9)	
Use of oral contraceptive pills, n(%)				
No	246	97 (14.5)	149 (14.7)	0.66
Yes	1277	515 (76.8)	762 (75.0)	
Missing	164	59 (8.7)	105 (10.3)	
Menopausal status at inclusion, n(%)				
Pre-menopausal	648	268 (39.9)	380 (37.4)	0.29
Post-menopausal	1039	403 (60.1)	636 (62.4)	

	Total (N = 1687)	Cases (n = 671)	Controls (n = 1016)	p-values†
Menopausal hormonal therapy use, n(%)^b				
Never used	399	156 (38.7)	243 (38.2)	0.03
Former user	227	80 (19.9)	147 (23.1)	
Current user	106	55 (13.7)	51 (8.0)	
Missing	307	112 (27.7)	195 (30.7)	
Chronotype				
Morning	845	350 (52.1)	495 (48.7)	0.10
Neutral	331	116 (17.3)	215 (21.2)	
Evening	511	205 (30.6)	306 (30.1)	

a: among parous women only, b: post-menopausal women only, † p-values derived from χ^2 for categorical variables, and Wilcoxon signed-rank test for continuous variables.

4.3. Night shift work

The prevalence of night work was 12.8% (n=217), with 13.4% among cases (n=90) and 12.5% among controls (n=127). The participants collectively held 314 night shift jobs comprising 79 with fixed schedules, 97 with alternating, and 139 with irregular schedules. Notably, 31 women held more than one type of night shift job during their occupational history. A detailed distribution of these jobs held by types, among cases and controls, can be found in Table 21. Most of these jobs were held for up to 5 years (55.9% among controls). The intensity of the jobs varied by type, with most fixed night shift jobs involving a higher frequency (>3 nights/week) and alternating and irregular schedules generally involving lower frequencies (< 3 nights/week). The distribution of night shift work by type of occupation can be found in Annex 21.

A detailed distribution of women by their case and control status, distinguishing between types of night shift work, can be found in Table 22. Varying patterns across night shift work types were observed when frequency and duration were assessed. Women with fixed night shift jobs worked more frequently, averaging 2 nights/week, while those with alternating and irregular schedules worked less frequently (<2 nights/week). Most women across all types held the jobs for 1-10 years, with those working for more than 20 years predominantly being engaged in alternating or irregular schedules. The distribution of the length of night shifts did not follow the same or a particular pattern across different types; however, women working alternating night shift schedules were likelier to work shifts shorter than 13 hours.

Table 21: Distribution of night shift jobs held in the C3-Nuit study nested within the CONSTANCES Cohort, 2012-2020.

	All night shift work (n = 314)		Fixed night shift work (n=79)		Alternating night shift work (n =97)		Irregular night shift work (n=139)	
	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
Duration of night shift work (years)								
≤5	73 (54.1)	100 (55.9)	23 (69.7)	25 (54.3)	24 (53.3)	28 (53.8)	27 (46.5)	47 (58.0)
6-10	28 (20.7)	36 (20.1)	8 (24.2)	10 (21.8)	7 (15.6)	7 (13.5)	13 (22.4)	19 (23.5)
10-20	14 (10.4)	21 (11.7)	2 (6.1)	6 (13.0)	3 (6.7)	8 (15.4)	9 (15.5)	7 (8.6)
> 20	20 (14.8)	22 (12.3)	-	5 (10.9)	11 (24.4)	9 (17.3)	9 (15.5)	8 (9.9)
Frequency (nights/week)								
<1	54 (40)	56 (31.3)	1 (3.0)	-	19 (42.2)	15 (28.9)	35 (60.3)	41 (50.6)
>1<3	51 (37.8)	80 (44.7)	5 (15.2)	7 (15.2)	26 (57.8)	37 (71.1)	20 (34.5)	36 (44.4)
≥3<5	18 (13.3)	24 (13.4)	16 (48.5)	20 (43.5)	-	-	2 (3.5)	4 (4.9)
≥5	12 (8.9)	19 (10.7)	11 (33.3)	19 (41.3)	-	-	1 (1.7)	0 (0)
Length of night shifts (hours)								
<8	10 (7.4)	8 (4.5)	3 (9.1)	-	-	-	8 (13.8)	8 (9.9)
≥8<10	30 (22.2)	34 (19.0)	6 (18.2)	8 (17.4)	14 (31.1)	14 (26.9)	10 (17.2)	12 (14.8)
≥10<12	41 (30.4)	48 (26.8)	17 (51.5)	13 (28.3)	18 (40)	26 (50)	6 (10.3)	9 (11.1)
≥12	54 (40)	89 (49.7)	7 (21.2)	25 (54.4)	13 (28.9)	12 (23.1)	34 (58.6)	52 (64.2)

ORs are based on fully adjusted models

Table 22: Night shift work in the C3-Nuit study nested within the CONSTANCES Cohort, 2012-2020.

	All night shift work		Fixed night shift work		Alternating night shift work		Irregular night shift work	
	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
Never	581	889	581	889	581	889	581	889
Ever	90	127	23	39	33	38	45	61
Frequency (nights/week)								
< 1.0	34 (37.8)	39 (30.7)	-	-	14 (42.4)	11 (28.9)	26 (57.8)	31 (50.8)
≥ 1.0<2.0	17 (18.9)	25 (19.7)	-	-	13 (39.4)	21 (55.3)	5 (11.1)	4 (6.6)
≥ 2.0<3.0	22 (24.4)	31 (24.4)	4 (17.4)	8 (20.5)	6 (18.2)	6 (15.8)	12 (26.7)	22 (36.1)
≥ 3.0	17 (18.9)	32 (25.2)	19 (82.6)	31 (79.5)	-	-	2 (4.4)	4 (6.6)
Duration (years)								
>1<10	45 (50.0)	73 (56.5)	18 (78.3)	25 (64.1)	18 (54.5)	20 (52.6)	22 (48.9)	40 (65.6)
≥10<20	22 (24.4)	26 (20.5)	5 (21.7)	8 (20.5)	3 (9.1)	7 (18.4)	13 (28.9)	11 (18.0)
≥20<30	10 (11.1)	13 (10.3)	-	3 (7.7)	4 (12.1)	5 (13.2)	6 (13.3)	5 (8.2)
≥30	13 (14.4)	15 (11.8)	-	3 (7.7)	8 (24.2)	6 (15.8)	4 (8.9)	5 (8.2)
Length of shift (hours)								
<10	27 (30)	35 (27.6)	6 (26.1)	18 (46.2)	12 (36.4)	13 (34.2)	14 (31.1)	18 (29.5)
≥10<13	39(43.3)	47 (37.0)	14 (60.9)	17 (43.6)	20 (60.6)	23 (60.5)	9 (20)	14 (23.0)
≥13	24 (26.7)	45 (35.4)	3 (13.0)	14 (35.9)	1 (3.0)	2 (5.3)	22 (48.9)	29 (47.5)
Total nights worked in lifetime (nights)								
<176.8	22 (24.4)	32 (25.2)	1 (4.3)	2 (5.1)	8 (24.2)	11 (28.9)	19 (42.2)	22 (36.1)
≥177<677	24 (26.7)	30 (23.6)	7 (30.4)	13 (33.3)	11 (33.3)	9 (23.7)	9 (20)	16 (26.2)
≥677<1724	23(25.6)	32 (25.2)	10 (43.5)	8 (20.5)	7 (21.2)	10 (26.3)	9 (20)	17 (27.9)
≥1724	21 (23.3)	33 (26.0)	5 (21.7)	16 (41.0)	7 (21.2)	8 (21.1)	8 (17.8)	6 (9.9)
Time since last night shift work (years)								
≤5	20 (22.2)	32 (25.2)	2 (8.7)	6 (15.4)	9 (27.2)	13 (34.2)	10 (22.2)	13 (21.3)
>5<20	32 (35.6)	45 (35.4)	6 (26.1)	14 (35.9)	8 (24.2)	13 (34.2)	21 (46.7)	22 (36.1)
≥20	38(42.2)	50 (39.4)	15 (65.3)	19 (48.7)	18 (54.5)	12 (31.6)	14 (31.1)	26 (42.6)

4.4. Association between night shift work and breast cancer risk

The OR and 95% CIs from the unconditional logistic regression models are depicted in Table 23, illustrating the estimates from three different models with the gradual adjustment of covariates. In Model 1, with basic adjustment for age at diagnosis, the OR for the association of breast cancer risk and night shift work (all types) was 1.08 (95% CI: 0.81-1.45). Further adjustment on reproductive and hormonal factors and lifestyle-related factors in Model 2 resulted in a negligible reduction in the OR and stayed unchanged on further adjustment on education used as a proxy for socio-economic status in Model 3 (OR: 1.06, 95% CI: 0.78-1.43).

The ORs in fully adjusted models (Model 3) showed that ORs associated with night shift work were notably higher in women working alternating schedules (OR:1.36, 95% CI: 0.85-2.27) than fixed or irregular schedules.

Table 23: Odds ratio and 95% confidence intervals for the association between night-shift work and breast cancer risk adjusting for different covariates in the C3-Nuit study nested within the CONSTANCES Cohort, 2012-2020.

Night shift work	Case/Control	Model 1	Model 2	Model 3
		OR (95% CI)	OR (95% CI)	OR (95% CI)
Never	581/889	Ref	Ref	Ref
Ever- all types	90/127	1.08 (0.81-1.45)	1.06 (0.79-1.43)	1.06 (0.78-1.43)
Ever-Fixed	23/39	0.91 (0.53-1.53)	0.92 (0.54-1.57)	0.91 (0.53-1.57)
Ever-Alternating	33/38	1.33 (0.83-2.15)	1.37 (0.84-2.24)	1.36 (0.83-2.23)
Ever-Irregular	45/61	1.13 (0.76-1.68)	1.07 (0.71-1.61)	1.07 (0.71-1.61)

Model 1: adjusted for age at diagnosis

Model 2: Model 1 + further adjustment on reproductive and hormonal factors (parity, age at first full-term pregnancy, breastfeeding, oral contraceptive use, maternal history of breast cancer, menopausal status, and menopausal hormonal therapy use) and lifestyle-related factors (alcohol, smoking, physical activity)

Model 3: Model 2 + further adjustment on education

4.4.1. Duration and intensity of night shift work and breast cancer risk

Table 24 presents OR and 95% CIs for the association between breast cancer risk and various exposure metrics of night shift work. Markedly, women working the longest duration (≥ 30 years) of alternating and irregular night shift works exhibited elevated ORs (alternating: 1.95, 95% CI: 0.65-5.81 and irregular: 1.14, 95% CI: 0.29-4.38) compared to non-night shift workers. However, for all night shift works combined, the OR was slightly lower (OR: 1.28, 95% CI: 0.59-2.77).

Regarding the ORs for frequency of night shift work, we did not observe a consistent trend in the ORs across different types of night shift work. Similarly, measuring intensity through the lengths of shifts, alternating night shifts, regardless of shift length, were associated with higher ORs compared to fixed or irregular night shift work, which showed predominantly increased ORs for shorter shifts. However, none of these estimates reached a statistical significance.

4.4.2. Cumulative exposure to night shift work and breast cancer risk

We did not find consistent evidence of the association between cumulative exposure assessed through total night shifts worked during the occupational history (Table 24). However, consistent with other metrics of intensity and duration, the cumulative exposure to higher ORs were found to be associated with the alternating night shift work.

4.4.3. Time since last night shift work

The latency of night shift work exposure measured through the time since quitting last night shift work did not show a consistent pattern of association with breast cancer risk (Table 24). Among those who terminated night shift work 20 years or more before diagnosis, elevated ORs were observed for fixed (OR:1.19, 95% CI: 0.58-2.41) and alternating night shifts (OR: 2.11, 95% CI: 0.96-4.64).

4.4.4. Consecutive nights worked

We also estimated ORs for breast cancer risk associated with the number of consecutive nights worked, focusing on alternating night shift work (Table 24). We found a more than twofold increase in OR when working fewer than three consecutive nights (OR of 2.73, 95% CI: 1.24-5.99).

Table 24: Odds ratio and 95% confidence intervals for the association between different metrics of night-shift work and breast cancer risk in the C3-Nuit study nested within the CONSTANCES Cohort, 2012-2020.

	All Night shift work		Fixed night shift work		Alternating night shift work		Irregular night shift work	
Categories	Case/Control	OR (95% CI)	Case/Control	OR (95% CI)	Case/Control	OR (95% CI)	Case/Control	OR (95% CI)
Never	581/889	Ref	581/889	Ref	581/889	Ref	581/889	Ref
Ever	90/127	1.06 (0.78-1.43)	23/39	0.91 (0.53-1.57)	33/38	1.36 (0.83-2.23)	45/61	1.07 (0.71-1.61)
Duration (years)								
Never	581/889	Ref	581/889	Ref	581/889	Ref	581/889	Ref
<10	34/65	0.91 (0.61-1.34)	18/25	1.13 (0.60-2.13)	18/20	1.39 (0.71-2.70)	22/40	0.78 (0.45-1.34)
≥10<20	22/26	1.30 (0.72-2.36)	5/8	0.97 (0.31-3.07)	3/7	0.79 (0.20-3.18)	13/11	1.82 (0.79-4.15)
≥20<30	10/13	1.10 (0.47-2.58)	-/3	-	4/5	1.25 (0.33-4.79)	6/5	1.73 (0.51-5.90)
≥30	13/15	1.28 (0.59-2.77)	-/3	-	8/6	1.95 (0.65-5.81)	4/5	1.14 (0.29-4.38)
Frequency (nights/week)								
Never	581/889	Ref	581/889	Ref	581/889	Ref	581/889	Ref
< 1.0	34/39	1.20 (0.74-1.94)	-	-	14/11	1.83 (0.82-4.12)	26/31	1.20 (0.70-2.08)
≥ 1.0<2.0	17/25	1.08 (0.57-2.06)	-	-	13/21	0.97 (0.47-2.01)	5/4	1.60 (0.42-6.12)
≥ 2.0<3.0	22/31	1.08 (0.61-1.90)	4/8	0.88 (0.26-3.02)	6/6	1.81 (0.56-5.87)	12/22	0.78 (0.38-1.62)
≥ 3.0	17/32	0.80 (0.44-1.48)	19/31	0.92 (0.51-1.67)	-	-	2/4	0.99 (0.18-5.47)
Length of shifts (hours)								
Never	581/889	Ref	581/889	Ref	581/889	Ref	581/889	Ref
<10	27/35	1.15 (0.68-1.94)	6/18	1.04 (0.34-3.15)	12/13	1.53 (0.68-3.45)	14/18	1.20 (0.58-2.46)
≥10<13	39/47	1.26 (0.80-1.98)	14/17	1.30 (0.62-2.70)	20/23	1.30 (0.69-2.44)	9/14	1.04 (0.44-2.46)
≥13	24/45	0.76 (0.45-1.28)	3/14	0.36 (0.10-1.29)	1/2	1.02 (0.09-11.47)	22/29	0.99 (0.55-1.79)

	All Night shift work		Fixed night shift work		Alternating night shift work		Irregular night shift work	
Categories	Case/Control	OR (95% CI)	Case/Control	OR (95% CI)	Case/Control	OR (95% CI)	Case/Control	OR (95% CI)
Total number of nights worked in lifetime (nights)								
Never	581/889	Ref	581/889	Ref	581/889	Ref	581/889	Ref
<176.8	22/32	1.02 (0.58-1.81)	1/2	0.91 (0.08-10.49)	8/11	1.28 (0.50-3.27)	19/22	1.23 (0.65-2.34)
≥177<677	24/30	1.19 (0.69-2.06)	7/13	0.88 (0.34-2.28)	11/9	1.84 (0.73-4.65)	9/16	0.84 (0.36-1.98)
≥677<1724	23/32	1.11 (0.64-1.96)	10/8	1.94 (0.74-5.06)	7/10	1.30 (0.48-3.55)	9/17	0.76 (0.33-1.76)
≥1724	21/33	0.96 (0.53-1.17)	5/16	0.48 (0.17-1.36)	7/8	1.56 (0.54-4.50)	8/6	1.93 (0.65-5.76)
Time since last night shift work (years)								
Never	581/889	Ref	581/889	Ref	581/889	Ref	581/889	Ref
≤5	20/32	1.04 (0.58-1.87)	2/3	0.59 (0.12-3.00)	9/13	1.12 (0.46-2.76)	10/13	1.31 (0.56-3.06)
>5<20	32/45	1.05 (0.65-1.70)	6/14	0.74 (0.28-1.97)	8/13	1.22 (0.49-3.02)	21/22	1.26 (0.67-2.36)
≥20	38/50	1.12 (0.71-1.75)	15/19	1.19 (0.58-2.41)	18/12	2.11 (0.96-4.64)	14/26	0.80 (0.41-1.56)
Consecutive nights worked								
Never					581/889	Ref		
<3 nights					18/11	2.73 (1.24-5.99)		
≥3- ≤4 nights					4/12	0.46 (0.14-1.49)		
>4 nights					11/15	1.46 (0.65-3.30)		

ORs are based on fully adjusted models

4.5. Night shift work and breast cancer risk stratified by menopausal status

Table 25 presents the estimates from the stratified analysis of the association of night shift work and breast cancer risk by menopausal status. There was no effect modification for any exposure metrics (p-value for interaction >0.05). The OR associated with night shift work was close to one in pre-menopausal women but slightly higher in post-menopausal women (OR 1.14, 95% CI: 0.79-1.66), which was possibly driven by an increased OR among alternating night shift workers (OR 1.66, 95% CI: 0.88-3.11). Longer duration of night shift work (≥ 10 years) and total nights worked in lifetime consistently exhibited elevated ORs among post-menopausal women. Among pre-menopausal women, higher ORs associated with higher frequencies (≥ 2 nights/week) were observed, whereas lower frequencies displayed higher ORs among post-menopausal women. However, none of the estimates for these metrics reached statistical significance. Among post-menopausal women who stopped working within the last 5 years before diagnosis, we observed an indication of a possible association (OR: 2.58, 95% CI: 1.00-6.66), while no similar association was found for those stopping night shift work more than 5 years ago before diagnosis.

4.6. Night shift work and breast cancer risk stratified by chronotype

We stratified the association of breast cancer risk and night shift work by chronotype, and the estimates are presented in Table 26. Among the three chronotypes, we observed higher ORs for women with morning chronotypes for engaging in any night shift work (OR: 1.31, 95% CI: 0.84-2.05). The estimates were particularly elevated for alternating night shift work among women with morning (OR: 1.82, 95% CI: 0.86-3.86) and neutral chronotype (OR: 1.98, 95% CI: 0.64-6.09) compared to the evening. Irregular night shift jobs had similar higher ORs among women with morning or evening chronotypes. Similar trends of elevated ORs persisted for morning chronotypes across other metrics such as frequency, duration of night shift work, lengths of shifts, and total nights worked.

Notably, higher ORs were observed among women who worked night shift jobs for more than 30 years and had morning chronotype (OR: 1.91, 95% CI: 0.53-6.82) or had neutral chronotype (OR: 2.73, 95% CI: 0.56-13.41) than evening chronotype, based on a small number of cases and

controls. Moreover, a positive association was identified among women with morning chronotype who worked between 176-675 nights in the entire occupational history (OR: 2.78, 95% CI:1.13-6.83).

Table 25: Odds ratio and 95% confidence intervals for the association between different metrics of night-shift work and breast cancer risk, stratified by menopausal status in the C3-Nuit study nested within the CONSTANCES Cohort, 2012-2020.

	Pre-menopausal		Post-menopausal		P for interaction
	Case/Control	OR (95% CI)	Case/Control	OR (95% CI)	
Night-shift					
Never	238/337	Ref	343/552	Ref	
Ever	30/43	0.96 (0.57-1.61)	60/84	1.14 (0.79-1.66)	0.67
Fixed	5/10	0.94 (0.30-2.94)	18/29	1.02 (0.54-1.90)	0.86
Alternating	12/13	1.35 (0.56-3.25)	21/25	1.66 (0.88-3.11)	0.85
Irregular	16/25	0.87 (0.44-1.74)	29/36	1.24 (0.73-2.09)	0.38
Duration (years)					0.87
Never	238/337	Ref	343/552	Ref	
<10	19/27	0.99 (0.52-1.91)	26/46	0.89 (0.54-1.49)	
≥10<20	7/10	1.20 (0.42-3.42)	15/16	1.59 (0.75-3.34)	
≥20<30	2/5	0.55 (0.10-2.99)	8/6	1.44 (0.52-4.02)	
≥30	2/1	1.35 (0.11-16.54)	11/14	1.36 (0.58-3.17)	
Frequency (nights/week)					
Never	238/337	Ref	343/552	Ref	0.76
<1.0	16/20	0.97 (0.47-2.01)	18/19	1.54 (0.78-3.04)	
≥1.0<2.0	3/7	0.74 (0.18-3.06)	14/18	1.36 (0.65-2.85)	
≥2.0<3.0	7/9	1.14 (0.39-3.32)	15/22	1.05 (0.53-2.09)	
≥3.0	4/7	1.13 (0.31-4.13)	13/25	0.80 (0.40-1.62)	
Length of night shift (hours)					0.07
Never	238/337	Ref	343/552	Ref	
<10	14/10	2.37 (0.98-5.74)	13/25	0.85 (0.42-1.73)	
≥10<13	11/18	0.89 (0.39-2.04)	28/29	1.64 (0.93-2.89)	
≥13	5/15	0.37 (0.13-1.12)	19/30	0.94 (0.51-1.74)	
Total nights worked in lifetime (nights)					0.67
Never	238/337	Ref	343/552	Ref	
<176.8	12/15	1.71 (0.51-2.69)	10/16	0.98 (0.43-2.24)	
≥177<677	9/11	0.98 (0.38-2.52)	16/21	1.27 (0.64-2.62)	
≥677<1724	6/9	1.09 (0.36-3.31)	17/23	1.16 (0.60-2.26)	
≥1724	3/8	0.57 (0.14-2.41)	17/24	1.13 (0.58-2.20)	
Time since last night shift work (years)					0.08
Never	238/337	Ref	343/552	Ref	
≤5	9/24	0.58 (0.26-1.31)	11/8	2.58 (1.00-6.66)	
>5<20	14/13	1.56 (0.69-3.55)	18/32	0.87 (0.47-1.61)	
≥20	7/6	1.35 (0.42-4.35)	31/44	1.11 (0.68-1.81)	

ORs are based on the fully adjusted models,

Table 26: Odds ratio and 95% confidence intervals for the association between different metrics of night-shift work and breast cancer risk, stratified by chronotype in the C3-Nuit study nested within the CONSTANCES Cohort, 2012-2020.

	Morning Chronotype		Neutral Chronotype		Evening Chronotype		P for interaction
	Case/Control	OR (95% CI)	Case/Control	OR (95% CI)	Case/Control	OR (95% CI)	
Night-shift							
Never	304/446	Ref	100/182	Ref	177/261	Ref	
Ever	46/49	1.31 (0.84-2.05)	16/33	0.83 (0.42-1.63)	28/45	0.86 (0.50-1.47)	0.72
Fixed	12/15	1.13 (0.50-2.53)	4/8	0.87 (0.24-3.21)	7/16	0.64 (0.35-1.66)	0.99
Alternating	17/14	1.82 (0.86-3.86)	7/8	1.98 (0.64-6.09)	9/16	0.80 (0.33-1.94)	0.92
Irregular	23/27	1.15 (0.63-2.10)	7/18	0.66 (0.25-1.65)	15/16	1.17 (0.54-2.54)	0.83
Duration (years)							
Never	304/446	Ref	100/182	Ref	177/261	Ref	0.95
<10	23/26	1.31 (0.71-2.41)	8/22	0.51 (0.21-1.26)	14/25	0.81 (0.39-1.68)	
≥10<20	15/13	1.46 (0.64-3.31)	3/4	2.22 (0.38-13.12)	6/9	0.98 (0.32-2.97)	
≥20<30	4/5	1.02 (0.25-4.18)	1/3	0.51 (0.04-5.90)	5/5	1.17 (0.30-4.54)	
≥30	6/5	1.91 (0.53-6.82)	4/4	2.73 (0.56-13.41)	3/6	0.61 (0.13-2.79)	
Frequency (nights/week)							
Never	304/446	Ref	100/182	Ref	177/261	Ref	0.44
< 1.0	18/14	1.68 (0.79-3.66)	5/12	0.66 (0.21-2.04)	11/13	1.02 (0.42-2.48)	
≥ 1.0<2.0	8/12	1.13 (0.44-2.92)	2/6	0.58 (0.10-3.31)	7/7	1.56 (0.50-4.82)	
≥ 2.0<3.0	13/11	1.77 (0.76-4.14)	6/9	1.34 (0.43-4.21)	3/11	0.32 (0.08-1.28)	
≥ 3.0	7/12	0.85 (0.32-2.28)	3/6	0.67 (0.43-3.05)	7/14	0.79 (0.29-2.12)	
Length of night shift (hours)							
Never	304/446	Ref	100/182	Ref	177/261	Ref	0.52
<10	14/13	1.85 (0.83-4.11)	5/13	0.50 (0.16-1.56)	8/9	1.02 (0.35-2.96)	
≥10<13	21/16	2.04 (0.99-4.20)	6/13	0.95 (0.33-2.77)	12/18	1.04 (0.46-2.36)	
≥13	11/20	0.67 (0.30-1.48)	5/7	1.25 (0.35-4.45)	8/18	0.62 (0.25-1.54)	
Total nights worked in lifetime (nights)							
Never	304/446	Ref	100/182	Ref	177/261	Ref	0.49
<176.8	13/11	1.55 (0.66-3.63)	2/10	0.29 (0.06-1.44)	7/10	0.97 (0.34-2.76)	
≥177<677	13/9	2.78 (1.13-6.83)	4/11	0.51 (0.15-1.75)	8/12	0.87 (0.33-2.30)	
≥677<1724	12/16	1.04 (0.46-2.35)	4/5	1.53 (0.36-6.54)	7/11	1.00 (0.35-2.82)	
≥1724	8/13	0.81 (0.32-2.07)	6/7	2.07 (0.60-7.22)	6/12	0.64 (0.21-1.92)	
Time since last night shift work (years)							
Never	304/446	Ref	100/182	Ref	177/261	Ref	0.95
≤5	11/13	1.30 (0.55-3.04)	3/7	1.19 (0.26-5.33)	6/12	0.93 (0.31-2.77)	
>5<20	15/17	1.28 (0.61-2.72)	6/10	0.89 (0.29-2.70)	11/18	0.75 (0.33-1.74)	
≥20	20/19	1.51 (0.76-2.99)	7/16	0.65 (0.24-1.73)	11/15	0.94(0.40-2.20)	

ORs are based on the fully adjusted models

4.7. Night shift work and breast cancer risk by time of initiation (before or after first pregnancy)

We explored whether the timing of initiation of night shift work relative to the first pregnancy influenced the association, and the estimates are presented in Table 27. The ORs associated with initiating night shift work after the first pregnancy were close to unity (OR: 0.84, 95% CI: 0.51-1.39), while initiating night shifts before the first pregnancy showed ORs slightly higher than one (OR: 1.09, 95% CI: 0.74-1.61), despite no statistical significance. A notably higher OR was found for alternating night shifts when it started before the first pregnancy (OR: 1.99, 95% CI:1.10-3.59).

Table 27: Odds ratio and 95% confidence intervals for the association between the night shift starting before or after the first pregnancy and breast cancer risk in the C3-Nuit study nested within the CONSTANCES Cohort, 2012-2020.

Night shift work	All night shift work		Fixed night shift work		Alternating night shift work		Irregular night shift work	
	Case/Control	OR (95% CI)	Case/Control	OR (95% CI)	Case/Control	OR (95% CI)	Case/Control	OR (95% CI)
Never	581/889	Ref	581/889	Ref	581/889	Ref	581/889	Ref
Starting after 1 st pregnancy	26/47	0.84 (0.51-1.39)	12/19	0.96 (0.45-2.04)	5/16	0.51 (0.18-1.42)	19/20	1.43 (0.74-2.76)
Nulliparous or starting before 1 st pregnancy	64/80	1.17 (0.82-1.66)	11/20	0.86 (0.41-1.86)	28/22	1.99 (1.10-3.59)	26/41	0.89 (0.53-1.49)

ORs are based on fully adjusted models

4.8. Sensitivity analyses using exclusive categories of night shift work

We conducted sensitivity analyses using the exclusive categories of night shift work. The ORs and the corresponding 95% CI are presented in Table 28. Similar to the findings in our main analyses, no statistical significance was achieved, but women who ever engaged in only alternating night shifts were found to have higher ORs 1.29 (95% CI: 0.74-2.25, Model 3) than those who only ever worked fixed or irregular schedules. Of note, for women who worked more than one type of night shift, the OR was remarkably higher (Model 3, OR: 1.82, 95% CI: 0.74-4.47).

Table 28: Odds ratio and 95% confidence intervals for sensitivity analysis of the association between night-shift work and breast cancer risk using exclusive categories of night shift work in the C3-Nuit study nested within the CONSTANCES Cohort, 2012-2020.

	Case/Control	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)
Never	581/889	Ref	Ref	Ref
Ever- all types	90/127	1.08 (0.81-1.45)	1.06 (0.79-1.43)	1.06 (0.78-1.43)
Fixed only	15/30	0.76 (0.41-1.43)	0.75 (0.39-1.43)	0.76 (0.40-1.44)
Alternating only	25/31	1.23 (0.72-2.11)	1.31 (0.75-2.27)	1.29 (0.74-2.25)
Irregular only	39/56	1.07 (0.70-1.63)	0.98 (0.63-1.51)	0.97 (0.63-1.50)
More than one type	11/20	1.68 (0.71-3.99)	1.87 (0.77-4.56)	1.82 (0.74-4.47)
Fixed and Alternating only	51/71	1.10 (0.76-1.60)	1.13 (0.77-1.65)	1.12 (0.76-1.65)

Model 1: adjusted for age at diagnosis, Model 2: Model 1 + further adjustment on reproductive and hormonal factors (parity, age at first full-term pregnancy, breastfeeding, oral contraceptive use, maternal history of breast cancer, menopausal status, and menopausal hormonal therapy use) and lifestyle-related factors (alcohol, smoking, physical activity), Model 3: Model 2 + further adjustment on education

Additionally, acknowledging the potential misclassification of irregular shift work as night shift work, we conducted a sensitivity analysis restricting to women who only worked fixed or alternating schedules (excluding irregular night shift work, n=95). Compared to the ORs for all types of night shift work combined (OR: 1.06, 95% CI: 0.78-1.43, Model 3), women who worked either fixed or alternating night shift work only had notably higher ORs in fully adjusted models (OR: 1.12, 95% CI: 0.76-1.65).

5. DISCUSSION

5.1. Summary of main finding

In this case-control study nested within a large French prospective cohort, we assessed several features of night shift work, such as duration, frequency, length of shift, and schedule types, in more details than ever. Our results did not exhibit a clear association of night shift with breast cancer risk, but we found some indicative association for alternating night shift work. Working fewer nights in succession with alternating schedules showed an augmentation in ORs compared to other metrics. Women initiating night shift work before their first pregnancy also displayed increased ORs. Stratification by menopausal status indicated a potentially higher risk among post-menopausal than in pre-menopausal women, and the stratified analyses by chronotype suggested a possible higher risk among women with morning chronotype. While our study does not significantly contribute to resolving ongoing inconsistencies in the existing literature, some of our findings warrant further investigations.

5.2. Comparison with literature

Our overall results regarding ever or never having worked night shifts do not corroborate with many case-control studies that have previously shown a positive association between night shift work and breast cancer risk^{154,156,159,161,168}. Despite the positive results, a common issue among these studies is the variability and inconsistency in the exposure assessment, which has also been a long-standing issue and a source of primary inconsistency in the existing literature¹⁴⁰. The definitions of night shift work vary significantly, ranging from working any number of hours between midnight and 5 am¹⁶¹ or at least an hour between midnight and 5 am¹⁵⁹ or working 8 hours between 7 pm and 9 am¹⁵⁴ or working a predominantly night shift jobs¹⁶⁸. Some epidemiological studies have assessed the exposure to night shift work solely using occupational titles and the industry or job matrix, which could have possibly resulted in the misclassification of the exposure^{156,168,261}. Some studies also used only the duration of exposure^{96,157,262,263} while others used multiple surrogate measures of circadian disruption such as intensity, length of shift, rotating nature, cumulative exposure, time of starting the first night shift job^{154,163,264–266}.

In this context of the wide heterogeneity in exposure assessment, our study adhered to the definition suggested in IARC's monograph on night shift work ¹³⁸. The largest case-control study, a pooled analysis of data from five countries (Australia, Canada, France, Germany, and Spain) ¹⁶³ used the same definition to address the limitation of heterogeneity of exposure assessment and reported an elevated breast cancer risk. However, the pooled analysis did not explore this observed association for types of night shift work.

Our study is among the few that presented the results for different types of night shift work based on specific schedules. The categorization of night shift work enabled us to assess the possible impact of differential levels of chrono disruption resulting from fixed, alternating, or irregular night shift schedules. The elevated ORs associated with alternating night shift works, particularly when working fewer than 3 consecutive nights, support the postulate that 'the fewer non-day shifts in succession, the lesser is the adaptation' ¹³⁸. With fewer consecutive nights, the body has less time to adapt to the non-day schedule before reverting to a regular or a different schedule, potentially resulting in a higher degree of chrono disruption and, consequently, a greater impact. Our findings regarding the alternating night shift work, characterized by rapid changes in work and sleep schedules over a week or month, can be particularly relevant if circadian disruption was indeed a contributing factor in the development of breast cancer. Our results align with a study in Denmark conducted among nurses ¹⁵⁴ that reported an increased breast cancer risk for rotating night shift work and with the Sister Study in the US ¹⁶⁹ that reported a positive association, particularly for individuals who worked rotating night shifts for 5 years or less. However, none of the studies evaluated the intensity of alternating night shift work in relation to consecutive nights worked.

Longer duration and higher intensity of night shift work have been frequently associated with elevated risk of breast cancer in many case-control as well as cohort studies ^{157,158,160,162,163,262}. Our study similarly observed notably higher ORs for a long-term night shift work of 20 years or more, particularly for alternating night shift work. Despite statistical insignificance, we observed notable variations between the types of night shift work. For instance, individuals involved in fixed night shift work tended to work higher frequencies and longer hours, while those in alternating shifts tended to work with lower frequencies and shorter shifts. Their corresponding ORs displayed an inconsistent trend across categories. These differences in trends across the types of night shift work possibly indicate varying impacts on the circadian

rhythm depending on intensity and type of schedule. Only a handful of studies explored the association of rotating or irregular types of night shift work ^{154,169,267} highlighting the need for further research into the specific shift types. Although, at this stage of analysis, we could not use detailed information on types of rotation, the availability of this information in our study provides a valuable opportunity for further exploration of our findings.

The Nurses' Health Study II ¹⁶⁰ reported a higher risk of breast cancer for younger women working at least 3 nights for 20 years or more. The pooled analysis by Cordina et al. reported that a long duration of night work over a lifetime (10 years or more), combined with high intensity (3 or more nights per week), was associated with an increased risk of breast cancer in pre-menopausal women ¹⁶³. The analysis based on the CECILE study ¹⁵⁹ showed an increased risk among women younger than 55 who worked an intense overnight job. Our study indicated a possible higher risk among post-menopausal women irrespective of the duration or intensity of night shift work. Interestingly, post-menopausal women currently working or who stopped working within 5 years preceding diagnosis displayed higher OR than those who had ceased night shift work much earlier. While it is often hypothesized that the carcinogenic effect of circadian disruption on breast tissues could be more pronounced in pre-menopausal women due to higher hormonal activity ⁴⁸, the inconsistencies in the findings suggest that the effect might be similarly significant in post-menopausal women.

5.3. Breast cancer risk and chronotype

Chronotype, which reflects the individual's circadian phase or diurnal preference (more morning or evening activities), has also been linked to the ability to adjust to non-daytime work schedules ²⁶⁸. Women with morning chronotypes might find it more challenging to adapt to night schedules, experiencing a greater circadian disruption due to the misalignment of their physiological inclination and their work schedule, compared to women with evening or neutral chronotypes ^{133,134}. The difference in the adaptability of different chronotypes to the night shifts may explain our findings of higher ORs among women with morning chronotypes. Our findings corroborate with the results of a Danish study, which demonstrated a higher risk for morning chronotype ¹⁵⁵. In contrast, in the MCC-Spain study ¹³⁴, higher ORs among women with morning or neutral were observed, similar to those results reported by a case-control study in Australia ¹⁶¹ and by Nurses' Health Study II ²⁶⁹.

Moreover, among women with morning chronotypes, we found elevated ORs for those who worked only for less than 10 or less than 20 years and a positive association among those who worked not more than 680 nights in their lifetime, a comparatively low number of nights. It can be argued that individuals with morning chronotype, facing more difficulties adapting to night work, are more likely to leave such jobs sooner, resulting in an overall shorter exposure¹³⁴. These findings corroborate the MCC-Spain study's findings, particularly for morning chronotypes with shorter exposure¹³⁴. However, it should be noted that the chronotype in our study was self-reported, and future studies could benefit from using a validated questionnaire to quantitatively assess the chronotypes, as utilized in the MCC-Spain study¹³⁴.

5.4. Latency of exposure

The positive association found in our study between breast cancer risk and initiation of night shift work before the first pregnancy, mainly the alternating type, is of particular interest as it supports the hypothesis that breast tissues before being completely differentiated (before pregnancy), are more susceptible to the potentially carcinogenic effects of circadian disruption,²²⁸ The higher ORs for alternating night shift work than other types further suggest that alternating schedules potentially cause higher circadian disruption and, thus, result in a higher risk of breast cancer. Our results align with those from the CECILE study¹⁵⁹ which reported an OR of 1.47 (95% CI:1.02–2.12) for night shift work commenced before the first full-term pregnancy and an even higher OR if started more than 4 years before the first pregnancy (OR: 1.95, 95% CI: 1.13–3.35). Other studies assessed latency of exposure by measuring the age when night shift work began, regardless of the timing of the first full-term pregnancy, but reported a null association. For instance, two studies^{261,264} reported no association for commencing night shift work between 21- 30 years of age, and one reported a similar null association for starting before 30 years²⁶⁶, these ages range typically being common for women to have their first pregnancy²⁶⁴.

5.5. Strengths and limitations

A key strength of this study was the careful classification and validation of each job period during the whole occupational history for every subject using the standard definition of night shift work suggested in the IARC's monograph. We also attempted to measure various features of night shift work exposure, such as frequency, duration, intensity, and type of schedule, to capture the diverse impact the night shift work might have on circadian rhythms.

The nested study design helps to limit the selection bias to a certain extent, enabling complete case ascertainment. Furthermore, case-control study design has been argued to be more appropriate and suitable than cohort studies for measuring complex exposures such as night shift work¹⁶⁷ Previously conducted case-control studies have consistently managed to assess more careful details of night shift work compared to cohort studies¹⁶⁷.

Moreover, our study, being nested within a general population-based cohort, encompasses women with a spectrum of jobs held over a lifetime, which addresses the limitation of heterogeneity in the study population in the existing literature. However, a lower prevalence of night shift work (12.8%) compared to the national prevalence (16.4% in 2015)¹⁴² and the inability to attain statistical significance still limit the generalizability of our findings.

Although our sample size is large enough, some of our estimates are based on small numbers of cases and controls, which may have resulted in limited statistical power. Our study is not exempt from the limitations of recall biases inherent to all case-control study designs. A retrospective examination of exposure based on self-reported occupational history may have led to exposure misclassification, and self-reported night shift work exposure over a long period may have a low validity^{270,271} with cases being more likely to remember the exposure in detail than controls²⁷¹. Nevertheless, self-reported occupational history is considered reliable and not a significant source of recall bias²⁷². Further, a prospective study with meticulous and comprehensive exposure assessment could provide more reliable results, addressing the limitations observed in current cohort studies to provide a precise measurement of night shift work exposure.

The lower prevalence of night shift work in our study could be partially attributed to lower participation rates, with participants more likely to have higher educational attainment and possibly a higher socio-economic status than non-participants. Due to less financial means and

lesser control over aspects of work, women with lower socio-economic status are more likely to be employed with unpredictable shifts (involving frequent night shifts) and are obliged to work unfavorable shifts like alternating or irregular^{273,274}. This under-representation of women with comparatively lower socio-economic status might have induced some extent of selection bias and a possible underestimation of risk. Moreover, in many epidemiological studies, these population groups are also the ones who are commonly missed out or not prioritized in studies on the effects of shift work¹⁴³.

Furthermore, our study did not have information on hormone receptor status for the cases due to a lack of access to the pathology reports at this stage of the study. The study has a relatively small number of cases resulting from a short follow-up period. At this stage of analysis, despite availability, we could not use the information on sleep and meal schedules, which co-occur with and may vary by the night shift work, resulting in possible residual confounding.

5.6. Conclusion

In this case-control study nested within a large French prospective cohort, we identified evidence indicative of a potential association between breast cancer risk and alternating night shifts. For other types of night shift work, even though assessed through several features, the associations were not definitive. Our results indicated a pronounced association for alternating night shift work initiated before the first pregnancy, for fewer nights were worked in succession with alternating schedules, and for women with morning chronotype. Our study addressed several limitations in existing literature, such as the variability in exposure assessment, using a detailed classification of night shift work with multiple exposure metrics. However, limited statistical power, recall bias, and potential residual confounding remain. Further analyses on details of alternating shifts, as well as considering additional factors like sleep and meal schedules, could provide more insight into how multiple chrono disruptors contribute to breast cancer risk. Future research using prospective study designs along with rigorous exposure assessments may help address the ongoing inconsistencies in the literature on breast cancer risk and night shift work exposure.

CHAPTER 5: GENERAL DISCUSSION

Rapid modernization and the increasing demand for services around the clock have rendered a considerable proportion of the world population more exposed than ever to outdoor LAN and night shift work. While these exposures are becoming inevitable, breast cancer incidence is also ever-increasing. Many experimental studies have suggested an intricate link between circadian disruption and breast cancer risk through multiple mechanisms. Exposure to LAN and night shift work are recognized factors for the dysregulation of circadian rhythm. In this thesis, we used three epidemiological studies in the French population to examine the risk of breast cancer due to exposure to outdoor LAN and night shift work used as proxies for circadian disruption. We examined this association closely while considering important confounding factors, possible effect modification by essential risk factors, and possible differences in risk by breast cancer subtypes.

5.1. Synthesis of main findings

The first and second objectives of this thesis focused on studying the association of outdoor LAN assessed using satellite images and breast cancer risk in two studies: CECILE, a population-based case-control study, and a case-control study nested within a large prospective cohort, the E3N-Generations cohort.

In the CECILE study, we found a suggestive association between exposure to outdoor LAN and breast cancer risk, which was similarly observed in the E3N-Generations cohort, where we identified a potential association between breast cancer risk and outdoor LAN exposure. The OR estimates were found to be of similar magnitudes in both studies and persisted even after adjusting for multiple confounders, including air pollution in the CECILE study and residential greenness in addition to air pollution in the nested case-control study.

Although neither study provided sufficient evidence on effect modification by menopausal status, both demonstrated augmented ORs for post-menopausal women. Results from the CECILE study was indicative of a potential association between outdoor LAN and breast cancer risk, particularly in urban areas. Meanwhile, in the E3N-Generations cohort, within urban areas, a tentative association was suggested, particularly in areas with lower residential greenness when compared to urban areas with higher greenness.

In the CECILE study, a stronger association was found for the HER2+ subtype than other tumor subtypes, while the association could not be explored in the E3N-Generations cohort due to the unavailability of complete information on HER2 receptor status.

The third objective of the thesis focused on studying the association between night shift work and breast cancer risk using C3-Nuit, a case-control study nested within a population-based cohort in France, CONSTANCES. We identified evidence that is indicative of a potential association between exposure to alternating night shifts and breast cancer risk. For other types of night shift work, several surrogate measures of night shift work were used, but the associations were not definitive. Stratification by menopausal status indicated a potentially higher risk among post-menopausal than in pre-menopausal women, while stratification by chronotype showed increased ORs for women with morning chronotype. Our results also indicated a pronounced association for alternating night shift work initiated before the first pregnancy.

Overall, this thesis provided evidence that may lend credence to the hypothesis that circadian disruption and the melatonin inhibition resulting from outdoor LAN and night shift work potentially play a role in augmented risk for hormone-dependent cancer like breast cancer.

5.2. Mechanism

The primary explanatory mechanism behind breast cancer risk associated with exposure to outdoor LAN and night shift work is circadian disruption, melatonin inhibition, and its downstream health effects. First suggested by Stevens in 2006, the 'circadian disruption hypothesis' posits that LAN-induced circadian disruption leads to suppressed melatonin production, thereby increasing the risk of hormone-dependent cancer like breast cancer ²⁴⁴. Our findings may lend credence to this "circadian disruption hypothesis." Although, in this thesis, we did not directly assess the circadian disruption, our findings, based on mere proxies like LAN and night shift work, provide potential support to this hypothesis.

Light is one of the primary cues for regulating circadian rhythm, and exposure to LAN from different environmental settings can alter the circadian phase and suppress the nocturnal melatonin production ²⁷⁵. Experimental studies have demonstrated that melatonin is associated with an inhibitory effect on mammary carcinogenesis ²⁷⁶. Inhibition of melatonin secretion due to exposure to LAN also interferes with estrogen receptor function, affects free radical biology,

and causes immunosuppression, thereby increasing the risk of breast cancer ¹²⁹. Night shift work is another significant cause of circadian disruption, involving exposure to high indoor and outdoor light and altered physical activity, alertness, meal, and sleep schedules ²⁷⁷. These exposures altogether contribute to the disruption in the body's natural circadian rhythm, thus increasing the risk of breast cancer.

Our findings of moderately augmented ORs associated with exposure to outdoor LAN lend plausibility to the hypothesis that LAN-induced circadian disruption could elevate breast cancer risk. Additionally, the suggestive association with alternating night shifts further indicates that circadian disruption due to night shift work is a potential causal factor in breast cancer.

With substantial evidence from experimental studies and limited evidence from human studies, night shift work was deemed a probable carcinogen (class 2A) by IARC in 2007- a classification reaffirmed in 2019 underscores the need for more robust human studies. Our findings, while adding to the available evidence, also suggest that the circadian disruption from exposures to LAN might extend beyond occupational settings to a broader population exposed to an increasing level of light pollution.

5.3. Comparison to existing literature

Night shift work and its association with breast cancer risk have been extensively studied over past decades, while the exposure to outdoor LAN is gaining increasing interest from the scientific community recently. Previously conducted epidemiological studies have often presented varied and sometimes conflicting results. Therefore, it is important to contextualize our findings within the existing epidemiological research to enhance the understanding, significance, and contribution to the field.

Exposure to outdoor LAN (assessed using satellite images) and breast cancer risk are studied by only a few epidemiological studies, five of which reported that women with the highest exposure to LAN had a minor but significantly augmented risk of breast cancer compared to the group with the lowest exposure ^{200,202–204,206}, while four studies showed no increase in risk related to LAN exposure assessed in the full range of visible light ^{182,199,201,205}. Similar to our studies in this thesis, the majority of the previous studies measured LAN exposure across the full spectrum of visible light from DMSP-OLS data, except the MCC-Spain Study ¹⁸², which

assessed light intensity from nighttime photographs taken by astronauts aboard the International Space Station (ISS). Compared to the lower resolution of DMSP images (~650m), ISS images used by the MCC-Spain study¹⁸² have higher resolution (30 m) and differentiate spectral components of visible light (blue, red, and green) allowing a more elaborate assessment of outdoor LAN. The MCC Spain study is the only study to date to have employed the ISS images to assess exposure to different wavelengths of visible light. They used the Melatonin Suppression Index (MSI), a proxy for blue light exposure, and demonstrated a higher risk of breast cancer while reporting no association for the total visible light.¹⁸² This finding supports the observation that blue light is the most effective spectral component of light for suppressing nocturnal melatonin production²⁵⁰ and could be linked with an elevated risk of breast cancer²⁴⁵.

Existing literature on exposure to LAN breast cancer risk exhibits a discordance depending on whether environmental confounders have been accounted for or not. The only two cohort studies considering other environmental exposures correlated with LAN that may confound the association^{199,201} have reported a null association. The Nurses Cohort Study in Denmark reported a decreased hazard ratio after adjustment for air pollution and road traffic noise¹⁹⁹; the US Sister Study cohort showed no association between LAN and breast cancer after adjustment for air pollution (NO₂, PM_{2.5}), noise pollution, and proximity to green spaces²⁰¹. In the CECILE study, we found that NO₂ exposure, a proxy for road-traffic-related air pollution, further reduced the ORs associated with outdoor LAN exposure.

However, in our nested case-control study in the E3N-Generations cohort, with a much larger sample size compared to the CECILE study, the estimates remained fairly unchanged, adjusting for significant environmental covariates, including air pollution and residential greenness (based on NDVI). The estimates from our study are comparable to those from 'The California Teacher's Study'²⁰⁰ reporting a hazard ratio of 1.12 (95% CI: 1.00, 1.26) for women exposed to the highest levels of LAN compared to the lowest, using a very comparable sample size (cases ~ 5000) during a similar follow-up period. Despite reporting positive estimates, the California Teacher's Study²⁰⁰ and others^{202–204,206} are still limited by their inability to consider the effect of other environmental exposures.

This divergence observed in the results between the studies based on whether or not environmental covariates were adjusted underscored the need to closely examine potential

confounding effects by such factors on the association between outdoor LAN and breast cancer risk. Our studies addressed this gap in the existing literature by adjusting for significant environmental covariates in our analyses and demonstrating elevated ORs.

In epidemiological studies, examining environmental exposures such as outdoor LAN in isolation is challenging as they amalgamate with other environmental exposures, notably air pollution. It is essential to exercise caution while considering other co-occurring exposures, such as air and noise pollution, as they could be highly correlated with outdoor LAN. In both studies, exposures to air pollutants were individually correlated with outdoor LAN. This issue was addressed by carefully adjusting for these exposures, considering the risk of variance inflation and bias in our statistical models. Despite the absence of variance inflation in the models, due to the high correlation between outdoor LAN, air pollution, and residential greenness, successfully disentangling these exposures in our data remained a challenge.

In addition, findings on slightly elevated ORs in urban areas (in CECILE) emphasize the relevance of outdoor LAN exposures in urban areas where numerous sources such as street lights, billboards, and traffic-related lights can result in higher levels of LAN exposure, along with urban factors such as lower greenness and higher air and noise pollution.

Following IARC's evaluation of night shift work as a probable carcinogen in 2007, numerous epidemiological studies have been conducted to explore this association further. Majority of the studies that reported a positive association case-control studies¹⁵⁴⁻¹⁵⁹, with a small number of cohort studies indicating similar risk^{96,160}. The results from meta-analyses have been also inconsistent. Some pooled analyses^{95,163,170} have suggested a moderately augmented risk of breast cancer among women as a result of exposure to night shift work, but others reported the contrary¹⁶⁴. One of the well-conducted pooled analyses of five case-control studies using the standardized definition to assess night shift work exposure indicated an overall increased risk of breast cancer among night shift workers, with an OR of 1.12 (95% CI: 1.00-1.25)¹⁶³. The study also noted that the risk increased with longer durations of night shift work (≥ 10 years) and higher intensity (≥ 3 nights/week)¹⁶³. A meta-analysis including 26 studies reported relatively lower pooled estimates for cohort studies for a longer duration of exposure (≥ 10 years: 1.01, 95% CI: 0.95–1.07) compared to those for case-control studies (≥ 10 years: 1.22, 95% CI: 1.02–1.46)⁹⁵.

Despite the growing body of literature, longstanding gaps persist, particularly in the inconsistent measurement of night shift work exposure, incomplete assessments, and heterogeneity in study populations, which were also recognized as major limitations in current epidemiological studies by the IARC's re-evaluation of carcinogenicity of night shift work in 2019⁹⁷.

Our third objective sought to address some of these gaps using the data from the C3-Nuit study. We adhered to IARC's suggestion of using a standardized definition for night shift work, defined as having worked at least three hours between midnight and 5 am, which is considered the minimum exposure needed to assess circadian phase disruption¹³⁸, while also using multiple measures to capture different features of night shift work. Despite a rigorous approach and employing multiple exposure metrics such as frequency, duration, cumulative exposure, our results did not exhibit a conclusive association between night shift work and breast cancer risk, which contrasts with previous case-control studies that have reported a positive association^{154,156,159,161,163,168}.

Nevertheless, we observed elevated ORs for alternating night shift work, mainly when working fewer nights in succession. Our study is one of the few^{154,169,267} exploring the association of night shift work by type of schedule. Our findings suggest that alternating shifts, due to the rapid changes in schedules, may pose a more significant challenge for circadian adaptation than fixed schedules, potentially leading to more significant circadian disruption and increased breast cancer risk. Additionally, we observed increased ORs among women with a morning chronotype, supporting the hypothesis that individuals with morning preferences may find it more challenging to adapt to night shifts¹³². The resulting misalignment between their circadian rhythms and work schedules could exacerbate the circadian disruption and associated breast cancer risk.

While our findings from the C3-Nuit study add valuable insights to the existing literature, particularly regarding the nature of night shift schedules and chronotype, they also contribute to the ongoing inconsistency in the overall association between night shift work and breast cancer risk.

5.4. Assessing circadian disruption in epidemiological studies

Globally, more than 80% of the population lives under a light-polluted night sky, and the night light emission is ever-growing – a trend also observed from our CECILE and E3N-Generations cohort data. Modernized lifestyles have made it nearly impossible to avoid light exposure at night. Simultaneously, the increasing demand for services and expansion of the global workforce has led to a side in the prevalence of night shift work. As these exposures become more pervasive with time, there is a growing concern about their potential public health implication concerning chronic diseases such as breast cancer. Thus, understanding the extent and impact of circadian disruption caused by these exposures is crucial.

Circadian disruption is inherently challenging to measure in epidemiological studies due to its complex nature. Direct assessment of circadian disruption typically requires detailed monitoring of biological markers, such as melatonin, core body temperatures, and cortisol levels. For instance, a study among hospital night shift workers assessed circadian disruption using several biomarkers²⁷⁸ and another study²⁷⁹ in a similar population by using sensors to assess chest-surface-temperature and activity levels, creating several indicators of circadian disruption such as rhythm index and rest profile. These indicators provided a quantitative measure of circadian disruption; however, small sample sizes and very short follow-ups limit their ability to establish long-term causal associations.

In large-scale epidemiological studies that require large sample sizes and extended follow-up periods, such direct assessment of circadian disruption is often not feasible. Consequently, assessing circadian disruption remains a challenging and complex endeavor in epidemiological studies. The most practical approach is to opt for proxies like night shift work and exposure to LAN, which can easily be measured through much simpler assessment methods.

Epidemiological studies on circadian disruptions and their effect on cancer risk predominantly focused on night shift work exposures. Night shift work encompasses a range of behaviors and environmental factors such as altered sleep patterns, activity levels, and meal timings—that collectively contribute to the misalignment of the internal circadian clock with external cues. European countries have observed a sharp increase in the prevalence of night shift workers¹⁴⁶ nearly doubling in less than a decade¹⁴⁸ which highlights both the relevance and opportunity for further studies on night shift work to produce robust and valid findings that can address

the longstanding gaps in the existing literature. Night shift work is compelling and relevant to the study; this exposure is fundamentally specific to certain occupational groups, limiting the findings' generalizability.

In contrast, exposure to LAN is a more pervasive factor affecting a broader population, transcending occupational boundaries. The widespread use of electric light, driven by modern societal demands, has led to an omnipresent exposure to LAN. This trend has been further exacerbated by the increasing adoption of energy-efficient LED lights, which emit higher levels of blue light—known to be particularly disruptive to circadian rhythms^{182,245,250}. In Europe, the transition to LED light began around the 2000s^{249,251}, along with the installation of more lights in streets over the past few decades¹⁸⁶. Other types of street lights used, including halogen lamps, fluorescent lights, and mercury vapor lights, that were in use before LED, have also been reported to emit a considerable proportion of blue light, causing melatonin suppression^{252,253}. These similarities in the blue light emissions from various sources, combined with the ongoing development of streetlights, underline the increasingly pervasive nature of LAN exposure.

This nature of exposure makes LAN a relevant measure for assessing circadian disruption at a population level. The increasing focus on LAN in epidemiological research reflects a growing recognition of its potential public health impact, particularly in the context of breast cancer risk.

5.5. Validity of the thesis

In this thesis, we utilized data from three case-control studies: one population-based, the CECILE, and two nested within large cohorts (the E3N-Generations cohort and the CONSTANCES). While these studies share a common objective within our thesis, they differ in key methodological aspects such as selecting cases and controls, sample size, exposure assessments, and analytical methods. These studies had several strengths, including objective measurement of outdoor LAN exposure, detailed assessment of night shift work, use of large sample sizes, and considering multiple possible confounders, which enhanced the internal validity of the findings. However, the validity of our thesis findings also hinges on other aspects of the methodological rigor of each study, with each potentially being subject to different types of biases. Thus, this section will address potential biases crucial for correctly interpreting our overall results and drawing a robust conclusion.

5.5.1. Selection bias

In each of our studies, variations in the selection procedures of cases and controls and differing participation rates could have potentially introduced selection bias, leading to distorted risk estimates²³². The possible selection biases in our studies have been discussed in the respective chapters: Chapter 2 (sections 5.3 and 5.4), Chapter 3 (sections 5.5. and 5.6), and Chapter 4 (section 5.5).

In the CECILE study, cases were more frequently selected from urban areas than rural, which could have led to a higher proportion of cases being exposed to outdoor LAN. Urban residence could signify higher exposure to outdoor LAN, and higher selection from urban areas results in the selection of cases not independent of the exposure status; this is a classic example of selection bias, where the selection of cases is not independent of exposure status and thus could have resulted in a biased estimate²³². This potential bias was mitigated by adjusting for urbanization in our analyses, though residual bias may have remained as other urban exposures, except for air pollution, were not fully accounted for.

In the case-control study nested within the prospective E3N-Generations cohort, all cases diagnosed during the follow-up period were included, and controls were individually matched with cases and selected using incidence density sampling. Controls were drawn from the same population as the cases, and the selection was independent of their exposure status²³².

Therefore, the likelihood of selection bias in this study is low, enhancing the internal validity of the findings.

Conversely, in the C3-Nuit study, the selection of cases and controls was marked by low participation rates—56% for cases and 64% for controls. Low participation rates can introduce bias if non-participants differ systematically from participants in ways that affect the exposure-disease relationship²³². As discussed in Chapter 4 (section 5.5), the observed differences in socioeconomic status and the likelihood that non-participants held more night shift jobs could have introduced bias into our risk estimates.

5.5.2. Information bias

In case-control studies, information bias can arise as differential or non-differential misclassification resulting from erroneous measurements of exposures, outcomes, or covariates²³². In this thesis, since we studied two different exposures using three studies with some variations in exposure, outcomes, and covariates assessment, the possible selection biases will be entailed in the following sections.

Outcome assessment

In our first two studies, CECILE and E3N-Generations nested case-control, all the cases were validated using pathology reports, making outcome misclassification unlikely. However, in the C3-Nuit study, while cases were validated using SNDS data, lack of access to pathology reports introduced a small possibility of outcome misclassification.

Exposure assessment

One of the main potential sources of information bias in this thesis is assessing exposure to outdoor LAN. For our first and second objectives, we used satellite images from the DMSP, which is widely employed in many epidemiological studies investigating the association between outdoor LAN and breast cancer risk. However, it has several recognized limitations, including low resolution, potential exposure saturation in urban areas, and non-differentiation between the spectral wavelengths¹⁸¹. These limitations could result in some degrees of exposure misclassification, particularly in urban areas where light intensity is higher and more variable. However, because this misclassification is likely non-differential—affecting both cases and controls equally—the resulting bias would generally attenuate the observed associations, biasing them toward the null rather than creating a spurious association.

Compared to the lower resolution of DMSP images (~650m), ISS images used by the MCC-Spain study¹⁸² have higher resolution (30 m) and differentiate spectral components of visible light (blue, red, and green) allowing a more elaborate assessment of through the use of Melatonin Suppression Index (MSI). Because of their higher resolution, these images provide enough variability in urban areas and allow measurements of different spectral components of light. Applying these images can address the limitation of potential exposure misclassification due to the low resolution of DMSP images.

A recent comparative study assessing outdoor LAN using DMPS, VIIRS, and ISS images²³⁰ argued that lower-resolution satellite images, like those of DMSP or VIIRS, have a higher likelihood of exposure misclassification and emphasized the importance of spectral differentiation for more accurate exposure measurement. However, during the periods of our studies (CECILE: 2005-2007, E3N-Generations: 1990-2011), ISS images were unavailable, making DMSP the only feasible source of satellite data. Nevertheless, we utilized radiance-calibrated, high-dynamic-range images, which provided adequate variability in exposure in urban areas (Hsu et al., 2015), addressing some limitations and reducing the risk of significant exposure misclassification.

In the C3-Nuit study, exposure to night shift work was assessed using a specifically designed questionnaire that collected detailed occupational histories. Although this information was gathered retrospectively, raising the possibility of recall bias—where cases might recall their occupational history more accurately than controls²⁷⁰, self-reported occupational histories are generally considered reliable and not a significant source of recall bias²⁷². In addition, careful classification of each job period during the whole occupational history also reduced the risk of exposure misclassification.

Covariate assessment

In the CECILE study, information on covariates was also collected retrospectively, introducing a potential for recall bias, whereas, in the case-control study nested in the E3N-Generations cohort, the information on covariates was collected regularly during the follow-up in the cohort, reducing the likelihood of recall bias. However, in the C3-Nuit study, even though the information was collected in the CONSTANCES cohort but pertaining to administrative purposes to be used in our analyses, only information on covariates at the time of inclusion

was available. Consequently, some crucial information, such as menopausal status at the time of diagnosis, was unavailable.

Moreover, SES in the CECILE and E3N-Generations cohorts was assessed using crude proxies, such as education level or occupation at the time of inclusion. These simplified measures may not fully capture the complexity of SES, leading to misclassification. However, it is unlikely that the misclassification was dependent on case-control status, as information was collected using similar methods for cases and controls.

In the first two objectives, the variables used for urbanization might not have fully captured the relevant aspects of urban exposure, leading to incomplete adjustment for confounding variables. Similarly, in the third objective, chronotype was assessed using crude, self-reported data, which is prone to misclassification. Since chronotype influences an individual's response to circadian disruption, misclassifying this variable could result in residual confounding, distorting the true relationship between night shift work and breast cancer risk.

5.5.3. Confounding bias

Breast cancer is a complex disease with multiple established risk factors. Although the primary exposures in this thesis were environmental and occupational, we adjusted for various possible confounders, including lifestyle-related, reproductive, or hormonal factors, carefully selected using DAGs. This approach was intended not only to reduce confounding bias but also to avoid overadjustment. In the analyses on outdoor LAN, we adjusted for air pollution in both the first and second objectives and residential greenness in the second. However, other crucial factors, such as exposure to indoor LAN and noise pollution, were unavailable in our studies.

Similarly, we did not account for other circadian disruptors, such as sleep or meal schedules, for the analyses on night shift work. These unmeasured or unadjusted variables, crucial to the studied associations, could have introduced some residual confounding. Some potential bias due to residual confounding, thus, remains.

5.5.4. Statistical power

All three studies used in this thesis had a sufficiently large sample size, particularly the nested case-control study in the E3N-Generations cohort, one of the largest studies assessing outdoor LAN and breast cancer risk. However, some of our positive estimates are based on small

numbers of cases and controls, such as those for the HER2+ tumor subtype in the CECILE study. In the C3Nuit study, the prevalence of night shift work was lower than anticipated, possibly due to low participation rates, leading to some underpowered subgroup analyses. The low numbers in some subgroups resulted in the estimation of imprecise ORs with wide CIs. This lower statistical power and imprecision challenge the validity of observed association or the lack thereof, thus raising concerns about whether these estimates accurately represent the true associations between outdoor LAN or night shift work and breast cancer risk or are merely artifacts of insufficient statistical power.

Following best practices in epidemiological research ^{280,281}, we did not rely on statistical significance to interpret the results in this thesis. Instead, the focus was on interpreting the OR estimates, emphasizing the magnitude or size of the effect and confidence interval, which represents the precision of the estimates. This approach was chosen over reducing the findings to a binary classification of significant or insignificant based solely on statistical significance.

Overall, while the studies in this thesis were robust and large-scale and contributed insights into the complex relationships of outdoor LAN and night shift work with breast cancer risk, thus adding evidence to ongoing research, various methodological challenges were encountered that need to be addressed adequately. Selection bias, information bias, and confounding bias have been carefully considered and mitigated where possible, but limitations remain. Despite these limitations, the comprehensive approach employed—leveraging large cohorts and carefully selected confounders, stratified analyses, and sensitivity analyses to ensure the robustness of findings — increases the validity of our findings and adds evidence to the growing body of literature on the potential impact of circadian disruption on breast cancer risk.

5.6. Generalizability of the results and public health implication

In the thesis, the results from the CECILE study, being population-based, are more broadly generalizable to a wider population. In contrast, the findings from the E3N-Generations cohort should be interpreted with caution, as the cohort predominantly included women engaged in teaching-related professions. Similarly, while the C3-Nuit was nested in a general population cohort, the findings are specific to occupations that involve night shift work, which may limit broader applicability.

However, the results on outdoor LAN exposure and breast cancer risk from the CECILE study suggest a particular relevance in urban areas. Given the higher relevance of LAN exposure in these areas, present findings could be generalizable to a broader population, especially considering the growing urbanization and increasing LAN exposure across diverse populations. Despite the difference in the populations studied, the evidence presented here remains relevant to the general population, particularly as outdoor LAN exposure is likely to have increased since the study period, making these findings even more pertinent. Similarly, with the increasing prevalence of night shift workers globally and in Europe, the results are noteworthy and underscore a broader public health implication.

The findings from our thesis carry potential significant public health implications. Even though these factors have not been established as causal exposures for breast cancer, our findings suggest possible association and, thus, warrant serious consideration in future research with implications at personal, organizational, and policy levels. Our findings also potentially underscore the need to develop strategies to mitigate circadian disruption in occupational and environmental contexts.

On an individual level, changes in personal behavior, such as reducing exposure to artificial LAN and maintaining regular sleep patterns, could help mitigate the exposure and the subsequent possible risk. At the organizational and policy levels, more stringent regulations on public lighting could be introduced, including restrictions on the hours of lighting and the types of light used in streetlights and billboards, such as those in some major cities in France^{282,283}. For night shift workers, institutional policies could be implemented to optimize shift schedules, regulate the number of rotations allowed, and ensure that workplace lighting is designed to minimize circadian disruption. Moreover, our results could contribute to

evaluating and categorizing these exposures as potential carcinogens by organizations such as IARC. Such a classification could significantly influence public health policies, leading to more informed decisions that better protect public health. By integrating these findings into policy discussions, we can contribute to a more comprehensive approach to cancer prevention in the context of modern environmental and occupational exposures.

5.7. Conclusion and perspective

Using three large epidemiological studies, this thesis evaluated the exposure to outdoor LAN and night shift work as proxies for circadian disruption and their association with breast cancer risk. This thesis provided evidence that outdoor LAN or night work may potentially be associated with the risk of breast cancer and possibly supporting the circadian disruption hypothesis. Our results might be more relevant in urban areas and specific night shift work schedules. However, the methodological limitations, potential selection biases, exposure misclassification, and residual confounding may undermine the validity of the observed associations. These findings, therefore, warrant confirmation through future studies with refined methodologies.

Despite the limitation posed by possible biases, careful and rigorous methods applied in this thesis lend credibility to our findings, contributing evidence to the growing body of literature on the potential impact of circadian disruption and breast cancer risk. Our findings convey important public health implications at multiple levels in light of rapid urbanization and the expanding global workforce. However, to acknowledge the limitations, further studies would require larger population-based samples with more refined, sophisticated, and comprehensive methods for exposure assessments over an extended period.

Further epidemiological research on outdoor LAN and breast cancer risk may benefit from large-scale, population-based studies with longer follow-up and more precise outdoor LAN measurements using ISS images to examine the association of breast cancer risk, especially with blue light exposure. Accounting for other factors, such as objectively measured indoor LAN exposures, crucial environmental factors, such as air pollution, noise pollution, and green spaces, could add insights into the complexity of the association. Such assessment can also incorporate exposure from using electronic devices at night and sleep and meal schedules.

Considering these exposures in further studies can allow a detailed exploration of the interplay of environmental and individual LAN exposures in breast cancer risk.

Future studies on night shift work should prioritize prospective longitudinal studies incorporating a detailed and standardized assessment of various aspects of night shift along with rigorous assessments of other circadian disruptors such as sleep and meal schedules. Such studies could offer insights into how multiple chrono disruptors contribute to breast cancer risk and help address the ongoing inconsistencies in the literature on breast cancer risk and night shift work exposure.

Furthermore, prospective study designs evaluating multiple exposures, including light at night, night shift work along with other occupational, environmental, and individual exposures, are essential to disentangle the independent and combined effects of these exposures, clarifying better the interplay between various factors in breast cancer risk related to night shift work and outdoor LAN exposure. Given the increasing interest of the scientific community in these topics and the increasing number of studies- some of which contribute to ongoing inconsistencies, a comprehensive meta-analysis of methodologically robust and high-quality studies is also required. Such analyses could provide a clearer understanding of the true association of these exposures with breast cancer risk.

Combined, such studies and analyses in the future could inform preventive and regulative measures that could assist in mitigating such exposures and ultimately reducing the associated risk of breast cancer.

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ANNEX

Annex 1: Summary of the case-control studies on night shift work and breast cancer risk.

Author	Exposure data source	Population characteristics	Definition of night shift work	Night shift work categories <i>Other metrics used</i>	Main Results	Covariates
Hansen and Lassen, 2012 ¹⁵⁵	Nationwide pension fund and Danish military's company registration 1990-2003, Denmark	Cases: 218 Controls: 899 Occupation : Millitray	Working during hours beginning after 5pm and ending before 9 am for at least 1 year, not including overtime	Ever/never <i>Duration</i> <i>Cumulative number of nights</i>	1.40 (0.90-2.10)	MHT, parity, age at menarche, education, occasional sun-bathing, tobacco smoking status
Hansen and Stevens, 2012 ¹⁵⁴	Danish nurses' association/ Danish Cancer Registry 2001-2003, Denmark	Cases: 310 Controls:1240 Age : <70 Occupation : Nurse	Graveyard shifts which worked after midnight (about 8 hours of work between 7 pm and 9 am) for at least 1 year	Ever/never <i>Duration of permanent night work</i> <i>Cumulative nights</i> <i>Rotating night shift work, types of rotation</i>	2.90 (1.10-8.00)	Age, family history of BC, MHT, number of mammograms
Li et al. 2015 ²⁸⁴	Textile Factory records, interviews, China	Cases: 1709 Controls: 4780 Occupation : Textile workers	Working at least once per week for at least 6 months between midnight and 6 am.	Duration (in years) <i>Cumulative number of nights</i>	0.99 (0.84-1.17)	Parity, live births, BF, alcohol
Rafnsson et al. 2003 ¹⁵⁶	Employment records/nationwide cancer registry, cabin attendant's cohort, Iceland	Cases: 35 Controls: 140 Occupation : Cabin attendant	Employed full-time ≥ 5 years; frequent long distance flights due to remote Iceland location	Duration: <5 years ≥5 years	Reference 5.24 (1.58-17.38)	Age, age at FFTP live births
Hansen, 2012 ¹⁶⁸	Nationwide Pension Fund, Danish Military Cohort, 1990-2003	Cases: 6281 Controls: 6024 Age : 30-50	≥ 6 months employment in a trade where ≥ 60% of women worked at night	Ever> 6 years /never	1.50 (1.30-1.70)	Age, age at FFTP and last childbirth, parity, SES
Fritschi et al. 2013 ¹⁶¹	Western Australian (WA) Cancer Registry/ Breast	Cases: 1205 Controls: 1789 Age : 18-80	Working for any number of hours between midnight and 5 am	Ever/never	1.16 (0.97-1.38)	Age, reproductive history, alcohol intake, smoking, physical activity and sleep, SES,

Author	Exposure data source	Population characteristics	Definition of night shift work	Night shift work categories <i>Other metrics used</i>	Main Results	Covariates
	Cancer Employment and Environment Study (BCEES) 2009-2011, Australia			<i>Duration</i> <i>Recent exposure</i> <i>Phase shift</i> <i>Sleep disruption</i>		remoteness of residence, family history of BC
Menegaux et al. 2012 159	CECILE study 2005-2007, France	Cases: 1232 Controls: 1317 Age : 25-75	Working for at least 1 hour between 11 pm and 5 am during all or part of each job	Ever/never <i>Overnight</i> <i>Duration, Frequency</i> <i>Night shift before first pregnancy</i>	1.27 (0.99-1.64) 1.35 (1.01-1.80)	Age, age at menarche, age at FFTP, parity, MHT, 1 st degree family history of BC, BMI, alcohol consumption, and tobacco consumption
Grundy et al. 2013 157	BC Cancer Registry (Vancouver), Hotel Dieu Breast Assessment Program (Kingston) 2005-2010, Canada	Cases: 1034 Controls: 1179 Age : 20-80	≥ 50% of time spent on evening and/or night shifts, capturing both rotating and permanent night shift schedules	Duration: None 0-14 years 15-29 years ≥30 years	Reference 0.95 (0.79-1.16) 0.93 (0.67-1.30) 2.21 (1.14-4.31)	Age, ethnicity; household income; education; menopausal status; use of fertility drugs, OC, non-steroidal anti-inflammatory drugs, antidepressants and MHT, parity, age at FFTP, BF and age at first mammogram; family history of BC among first-degree relatives; smoking, alcohol consumption; BMI
Pesch et al. 2010 264	Telephone interview GENICA study 2000-2004, Germany	Cases: 857 Controls: 892 Age : ≤80	Working the full-time period between midnight and 5 am	Ever/ Never <i>Cumulative number of lifetime night shifts</i> <i>Duration Age at first night shift work</i> <i>Years since last night shift</i>	1.01 (0.68-1.50)	Age, family history, MHT, mammograms
O'Leary et al. 2006 285	Electromagnetic Fields and Breast Cancer on Long Island Study 1996-1997, US	Cases: 576 Controls: 585	Overnight shift starting as early as 7 pm and continue until the following morning	Ever/never <i>Frequency</i> <i>Duration</i>	1.04 (0.79-1.38)	Age, parity, family history, education, benign breast disease

Author	Exposure data source	Population characteristics	Definition of night shift work	Night shift work categories <i>Other metrics used</i>	Main Results	Covariates
Davis et al. 2001 158	Cancer Surveillance System of the Fred Hutchinson Cancer Research Center, Seattle, WA, 1992-1995, US	Cases: 763 Controls: 741 Age : 20-74 Occupation :	Graveyard shift beginning after 7 pm and leaving work before 9 am	Ever/never <i>Frequency</i> <i>Duration</i> <i>No peak sleep</i> <i>Light at night</i>	1.60 (1.00-2.05)	Parity, family history, OC use, recent MHT
Papantoniou et al. 2015 167	MCC-Spain Study 2008-2013	Cases: 1708 Controls: 1778 Age : 20-85	Working partly or entirely between midnight and 6 am at least three nights per month. Including overnight, late evening (end after midnight) and early morning (start before 6am)	Eve/Never <i>Types</i> <i>Duration</i> <i>Cumulative number of nights</i> <i>Chronotype</i>	1.18 (0.97-1.43)	Age, family history, education, marital status, BMI, Tobacco smoking, physical activity, sleep habits, diet habits, Menopausal status, Parity, age at FFTP, BF, ever OC, MHT, past sun exposure
Santi et al. 2015 286	Population-based case-control breast cancer study Canada	Cases: 743 Controls: 775 Occupation : Nurses	Nurses who worked in hospitals	Ever/never <i>Duration > 10 years</i>	1.65 (1.04-2.26) 1.70 (1.04-2.79)	Age, family history, level of education, OC use, alcohol consumption, parity, and age at menarche
Lie et al. 2013 287	Cancer Registry Norway 1990-2007, Norway	Cases: 172 Controls: 474 Age : 35-75 Occupation : Nurses	Working between midnight and 6 am	Duration and intensity : Never worked night shift <consecutive night Worked <5 years & ≥6 consecutive nights Worked ≥5 years & ≥6 consecutive nights	ER+ : Reference 1.2 (0.9-1.8) 1.3 (0.8-2.0) 1.8 (1.0-3.1) ER-: 2.0 (0.8-4.8) 1.7 (0.6-4.8) 2.8 (0.8-9.2) PR+ :	Age at diagnosis, period of diagnosis, parity, 1 st degree family history of BC, recent MHT, and frequency of alcohol consumption at the time of diagnosis

Author	Exposure data source	Population characteristics	Definition of night shift work	Night shift work categories <i>Other metrics used</i>	Main Results	Covariates
					1.3 (0.9-2.0) 1.4 (0.9-2.4) 2.4 (1.3-4.3) PR-: 1.4 (0.8-2.4) 1.2 (0.7-2.3) 1.2 (0.5-2.8)	
Pham et al. 2019 ²⁶⁶	Breast Cancer Center or Health Examination Center at the National Cancer Center, 2012 -2018, Korea	Cases: 1721 Controls: 1721 Age : >20	Working regularly between 9 pm and 8 am for at least 2 months in their lifetime	Ever/Never <i>Age at first night shift work</i> <i>Days/ week</i> <i>Time of start: before or after midnight</i> <i>Duration</i> <i>Cumulative frequency lifetime</i>	1.10 (0.88-1.39)	Age, educational level, parity, age at FFTP, body mass index, age at menarche, alcohol consumption, smoking, hormone treatment, 1 st degree family history of BC

BMI: Body-mass Index, ER: Estrogen Receptor, FFTP: First full-term pregnancy, MHT: Menopausal hormonal therapy, OC: Oral contraceptive, PR: Progesterone Receptor, SES: Socio-economic status

Annex 2: Summary of the cohort studies on night shift work and breast cancer risk.

Author	Study name/ Data source	Population characteristics	Definition of night shift work	Night shift work categories and additional metrics	Main Results	Covariates
Koppes et al. 2014 ²⁶⁷	Dutch Labor Force Surveys/ National Medical Registration 1996-2009, Netherlands	Total: 285,723 Cases: 25317 Follow-up: Mean 7 years Age : 15-65	Work between midnight and 6 am	Never Regular Occasional <i>Duration</i> <i>Hours/week</i>	Reference 1.04 (0.85-1.27) 0.87 (0.72-1.05)	Age, origin, children in the household, education, occupational group, contractual working hours, and job tenure
Pronk et al. 2010 ²⁶¹	Shanghai Women's Health Study 1996-2000	Total: 73,049 Cases: 7179 Follow up: Mean 9 years Age : 40-70	Starting work after 10 pm at least 3 times a month for over 1 year	Ever/Never Using job exposure matrix Self-reported <i>Frequency</i> <i>Duration</i> <i>Cumulative exposure</i> <i>Age at starting night-shift work</i>	1.00 (0.20-1.20) 0.90 (0.70-0.10)	Age, age at FFTP, parity, family history, education, work-related PA
Åkerstedt et al. 2015 ²⁶²	Swedish Twin registry/ Swedish Cancer Registry, 1998-2010	Total: 13,656 Cases: 463 Follow-up: 12 years Age : 41-60	Working hours in nights at least now and then	Ever/Never <i>Duration of night shift work</i>	0.96 (0.74-1.24)	Age, education, parity, Tobacco use, BMI, PA, Alcohol consumption, coffee consumption, menopause status, MHT, previous cancer, time to BC diagnosis
Wegrzyn et al. 2017 ¹⁶⁰	Nurses' Health Study II 1989-2003, US	Total: 114,559 Cases: 3570 Follow up: 24 years Age : 30-55 Occupation : Nurses	At least 3 nights/month in addition to days or evenings in that month	Duration None 1-9 years 10-19 years ≥20 years	Reference 1.04 (0.96-1.12) 0.94 (0.81-1.10) 1.40 (1.00-1.97)	Age, height, BMI, adolescent body size, age at menarche and FFTP, parity, BF history, type of menopause, age at menopause, MHT use, duration of types of MHT, 1 st degree family history of BC, history of benign breast disease, alcohol consumption, physical activity, and current mammography use

Author	Study name/ Data source	Population characteristics	Definition of night shift work	Night shift work categories and additional metrics	Main Results	Covariates
Jones et al. 2019 ²⁸⁸	Generations Study cohort 2003-2014, UK	Total: 102,869 Cases: 2059 Follow-up: Median 9.5 years Age : >16	Working in evening or night (between 10 pm and 7 am)	Ever/never <i>Intensity : Hours/night</i> <i>Frequency : nights/week</i> <i>Duration</i> <i>Cumulative hours</i>	1.00(0.86–1.15)	Alcohol use, parity, OC use, MHT use, and menopausal status
Travis et al. 2016 ¹⁶⁴	EPIC-Oxford study 1993–1999, UK	Total: 22,559 Cases: 181 Follow-up: Mean 3 years	Any job lasting for at least one year, and occurring on a regular basis for at least one night per month or 12 nights per year	Ever/never Duration >20 years	1.07 (0.71-1.62)	Age, SES, marital status, nulliparity, age at FFTP, number of children, obesity, physical activity, alcohol consumption, smoking, first-degree relative with BC, OC use, MHT use, amount of sleep, take medication to sleep, chronotype
Travis et al. 2016 ¹⁶⁴	Million woman study 1996 – 2001, UK	Total: 522,246 Cases: 4809 Follow-up: Mean 2.6 years	Any time between midnight and 6 am for at least 3 nights per month	Ever/never <i>Duration</i>	1.00 (0.92-1.08)	Age, SES, marital status, nulliparity, age at FFTP, number of children, obesity, physical activity, alcohol consumption, smoking, first-degree relative with BC, OC use, MHT use, amount of sleep, take medication to sleep, chronotype
Travis et al. 2016 ¹⁶⁴	UK Biobank 2006-2010	Total: 251,045 Case: 67 Follow-up: Mean 3.8 years	Any substantial night work for	Ever/never	0.78 (0.61-1.00)	Age, SES, marital status, parity, age at FFTP, number of children, obesity, physical activity, alcohol consumption, smoking, first-degree relative with BC, OC use, MHT use, amount of sleep, sleep medication, chronotype

Author	Study name/ Data source	Population characteristics	Definition of night shift work	Night shift work categories and additional metrics	Main Results	Covariates
Sweeney et al. 2020 ¹⁶⁹	Sister study cohort 2003–2009, US	Total: 48,451 Case: 3191 Follow-up: Mean 9 years	1 hour between midnight 2 am for ≥ 2 years	Ever/never Rotating night shift work Irregular night shift work <i>Duration in years</i>	1.08 (0.92–1.27) 0.98 (0.91–1.06)	Age, ethnicity, education, marital status and parity

BMI: Body-mass Index, FFTP: First full-term pregnancy, MHT: Menopausal hormonal therapy, OC: Oral contraceptive, SES: Socio-economic status

Annex 3: Summary of the studies on outdoor LAN and breast cancer risk.

Author, Year	Study name	Population Characteristics	Outdoor LAN assessment methods	Breast cancer risk estimates (HR/OR)*		Covariates
Cohort studies						
Clarke, 2021 ¹⁹⁹	Danish Nurse Cohort (1993-2012), Denmark	Cases: 745 Sample size: 28731 Person years: 320,289 Follow up duration: 17.1 years Age: ≥ 44 years Occupation: Nurses	Data sources: DMSP Duration: 1996-2010 Geocoded addresses: Yes Residential history: Yes	Categorical: T1 (0-21.9 nW/cm ² /sr) T2 (22.0-65.7 nW/cm ² /sr) T3 (65.8-446.4 nW/cm ² /sr) Continuous: LAN per IQR increase (71.7 nW/cm ² /sr)	T1: Reference T2: 1.09 (0.90-1.31) T3: 0.97 (0.77-1.23) 0.92 (0.83-1.02)	Age calendar year, entry at baseline, birth cohort, urbanicity, alcohol consumption, marital status, night shift work, road traffic noise, PM _{2.5} , NO ₂ , green spaces
Hurley, 2014 ²⁰⁰	California Teachers Study Cohort, United States (1995/96-2011)	Cases: 5,095 Sample size: 106731 Follow up period: 1995-96 to 2010/ to date of diagnosis, death/ moving out of California) Age: 20-70 years Occupation: school employees	Data sources: DMSP Duration: 2006 only Geocoded address: Yes Residential history: No	Categorical: Q1 (0-14.2 nW/cm ² /sr) Q2 (14.3-26.4 nW/cm ² /sr) Q3 (26.5-37.4 nW/cm ² /sr) Q4 (37.5-53.3 nW/cm ² /sr) Q5 (53.5-175.2 nW/cm ² /sr)	Q1: Reference Q2: 1.05 (0.95-1.16) Q3: 1.06 (0.95-1.17) Q4: 1.05 (0.95-1.17) Q5: 1.12 (1.00-1.26)	Age at baseline, race/ birthplace, family history of breast cancer, age at menarche, age at first full-term pregnancy, breast feeding history, physical activity, body mass index, alcohol consumption, menopausal status and menopausal hormone therapy, smoking SES and urbanization

Author, Year	Study name	Population Characteristics	Outdoor LAN assessment methods	Breast cancer risk estimates (HR/OR)*		Covariates
James, 2017 ²⁰³	Nurses' Health Study II Prospective cohort, United States (1989–2013)	Cases: 3,549 Sample size: 109,672 Follow up: 1989–2013 Person years : 2,187,425 Age: 25-42 years, Occupation: Registered nurses	Data sources: DMSP Duration: 1989-2011 Geocoded address: Yes Residence history: Yes	Categorical: Q1 (Median 4.3 nW/cm ² /sr) Q2 (Median 12.4 nW/cm ² /sr) Q3 (Median 22.9 nW/cm ² /sr) Q4 (Median 37.2 nW/cm ² /sr) Q5 (Median 64.0 nW/cm ² /sr) Continuous: per IQR increase	Q1: Reference Q2: 1.05 (0.94-1.18) Q3: 1.01 (0.90-1.13) Q4: 1.08 (0.97-1.22) Q5: 1.14 (1.0-1.29) Per IQR: 1.05 (1.00-1.11)	Age, calendar year, race, benign breast cancer history, family history of breast cancer , BMI, personal income, parity and age at first birth, height, weight, menopausal status, oral contraceptive use, mammography screening, smoking status, marital status, living alone, night shift work, diet, physical activity
Xiao, 2020 ²⁰²	NIH-AARP Diet and Health Study Cohort (1996-2011) United States	Cases: 2562 Sample size: 86773 Follow up: 2005-2011 Menopausal women	Data sources: DMSP images Duration: 1996 Geocoded address: yes Residential history: Yes: but for only those who stayed with in 1km of initial address at baseline	Categorical (median [IQR]): Q1: 4.2 (2.4-6.3) nW/cm ² /sr Q2: 13.3 (10.8-16.1) nW/cm ² /sr Q3: 26.9 (23.0-31.0) nW/cm ² /sr Q4: 45.7 (40.6-51.5) nW/cm ² /sr Q5: 76.6 (66.6-90.3) nW/cm ² /sr Continuous: Per quintile increase	Categorical Q1 Reference Q2: 1.01 (0.95-1.07) Q3: 1.06 (1.00-1.13) Q4: 1.09 (1.02-1.16) Q5: 1.10 (1.02-1.18) Continuous 1.02 (1.01-1.04)	State of residence, ethnicity, education, marital status, breast cancer diagnosis in first-degree relatives, age of menarche, age at first childbirth, contraceptive use, age at menopause, menopause hormonal therapy, smoking status, physical activity, alcohol consumption, number of breast biopsies, mammogram in the past 3 years, healthy eating index, census tract median home value, poverty rate and population density.

Author, Year	Study name	Population Characteristics	Outdoor LAN assessment methods	Breast cancer risk estimates (HR/OR)*		Covariates
Xiao, 2021 ²⁰⁴	Southern community Cohort United States, (2017-2021)	Cases: 233 Sample size: 43500 Person years: 490613	Data sources: DMSP Duration: 2002-2009	Categorical (median [IQR]): Q1: 1.2 (0.8-1.7) 10nW/cm ² /sr Q2: 6.2 (3.8-9.1) 10nW/cm ² /sr Q3: 20.3 (16.3-24.3) 10nW/cm ² /sr Q4: 35.9 (32.3-39.5) 10nW/cm ² /sr Q5: 55.6 (48.9-68.2) 10nW/cm ² /sr Continuous:	Categorical Q1: Ref Q2: 0.98 (0.82-1.18) Q3: 1.13 (0.93-1.36) Q4: 1.01 (0.82-1.25) Q5: 1.27 (1.00-1.60) Continuous Overall: 1.03 (1.01-1.06) Black: 1.04 (1.00-1.07) White: 1.03 (0.96-1.11)	Age, education, marital status, income, health insurance coverage, family history of breast or ovarian cancer, mammogram, smoking status, number of live births, age at first birth, age at menarche, menopausal status, menopausal hormone therapy, alcohol consumption, population density, poverty.
Sweeney, 2022 ²⁰¹	Sister Study Cohort (2003-2015) United States	Cases: 3734 Sample size: 47145 Follow up: 8-13 years Duration: 2003-2019 Age: 35-70 years, having sister diagnosed with breast cancer	Data sources: DMSP Duration: 2006-2009 Geocoded address: Yes Residential history: Yes	Categorical: Q1 ≤27.55 nW/cm ² /sr Q2 ≤90.85 nW/cm ² /sr Q3 ≤176.20 nW/cm ² /sr Q4 ≤278.50 nW/cm ² /sr Q5 ≤2776.52 nW/cm ² /sr	Q1: Reference Q2: 0.99 (0.88-1.11) Q3: 0.97 (0.85-1.10) Q4: 0.99 (0.86-1.14) Q5: 0.89 (0.74-1.06)	Race, education, income, area deprivation index , latitude, population density for models with indoor light , air pollution (PM _{2.5} , NO ₂), NDVI and noise pollution
Case-control studies						
Keshet-Sitton, 2017 ²¹¹	Case controls study, Israel (2010-2014)	Cases: 93 Controls: 278 Age : 29-91 years Jewish, non-shift workers	Data sources: Questionnaire on sleep habits Duration: 10-15 years before the diagnosis /interviews	Residing near strong LAN source	1.52 (1.10-2.12)	Age and residential area, reproductive factors, and sleep habits

Author, Year	Study name	Population Characteristics	Outdoor LAN assessment methods	Breast cancer risk estimates (HR/OR)*		Covariates
Bauer, 2013 ²⁰⁶	Case-cohort study based on Georgia Comprehensive Cancer Registry (2000-2007)	Cases: 33503 Controls: 47817 Age: Not reported	Data sources: DMSP 1992–2007 Duration: 9-16 years (1992 to 2002/7) Geocoded address: Yes Residential history: No	Categorical: Low (0-20 W/cm ² /sr) Medium (21-41 W/cm ² /sr) High (>41 W/cm ² /sr)	Low : Reference Medium:1.06 (0.97-1.16) High: 1.12 (1.04-1.20)	Race, tumor grade and stage, year of diagnosis, age at cancer diagnosis, Metropolitan Statistical Area (MSA) status, births per 1,000 women aged 15–50, MSA population mobility, population over 16 in the labor force, and prevalence of smoking
Garcia-Saenz, 2018 ¹⁸²	Multi case control study Spain (2008-2013)	Cases: 490 Controls: 380 Age: 20-85 years Non-night shift workers	Data sources : ISS images Duration: 01-2014 Geocoded addresses: Yes Residential history: Yes, but LAN assessed at longest stayed address	Visual Light: T1 :0.01-0.05 cd/m ² T2: 0.05-0.07 cd/m ² T3: 0.07-0.23 cd/m ² Blue light using Melatonin Suppression Index (MSI): T1: 0.04-0.13 T2 : 0.13-0.16 T3: 0.16-0.41	Visual Light: T1: Reference T2: 0.87 (0.60-1.24) T3: 0.81 (0.54-1.20) Blue light using MSI T1: Reference T2: 0.91 (0.62-1.32) T3: 1.47 (1.00-2.17)	Age, sex, center, educational level, socioeconomic status, Urban Vulnerability Index, BMI, tobacco, family history of breast cancer, chronotype, menopausal status and mutual adjustment for other light exposures.
Kloog, 2011 ²⁰⁸	Breast cancer in Northern Israel Case control study (2000-2008)	Cases: 794 Controls: 885 Age: Case: 58.89 years Control: 60.86 years	Data sources: Individual interview on sleep settings	Bedroom shutters open	0.82 (0.66-1.01)	Age, location of primary clinic, and ethnicity, alcohol consumption, number of births, religion, age, and education, family history of cancer, parity, oral-contraceptive use, and menopausal hormonal therapy.

Author, Year	Study name	Population Characteristics	Outdoor LAN assessment methods	Breast cancer risk estimates (HR/OR)*		Covariates
Li, 2010 ²⁰⁹	Case control study, United States (1994-1997)	Cases: 363 Controls: 356 controls Age: 31-85 year	Data sources: In-person interviews on sleep settings Duration: 10 years before the diagnosis/interview	Outdoor light entering the sleeping area	Premenopausal: 1.0 (0.5-1.8) Postmenopausal: 1.1 (0.8-1.7)	Age group, race, BMI, age at first menstrual period, family history of breast cancer, age at first full-term birth, months of lifetime breast feeding, cigarette smoking, and alcohol drinking
Ritonja, 2020 ²⁰⁵	Case control study based on British Columbia Cancer Registry, Canada, (2005-2010)	Cases: 844 Controls: 905 Age: 40-80 years	Data sources : DMSP VIIRS DNB images Duration: 5-20 years prior to the diagnosis/interview Geocoded address: Yes Residential history: Yes	VIIRS DNB T1: 0.00-2.07 nW/cm ² /sr T2: 22.08-32.79 nW/cm ² /sr T3: 32.83-149.47 nW/cm ² /sr DMSP T1: 0.00-123.05 nW/cm ² /sr T2: 123.10-194.62 nW/cm ² /sr T3: 194.75-628.56 nW/cm ² /sr	VIIRS DNB T1: Reference T2: 0.97 (0.75-1.26) T3: 0.95 (0.70-1.27) DMSP T1: Reference T2: 1.05 (0.82-1.34) T3: 0.83 (0.63-1.09)	Age, ethnicity, family history of breast cancer, menopausal status, age at menarche, BMI, household income, education, parity and age at first birth, oral contraceptive use, age at first mammography screening, smoking, night work status, alcohol consumption, population density, neighborhood income

DMSP: Defense Meteorological Satellite Program, DNB: Day-night Band, HR: Hazard Ratio, ISS: International Space Station, IQR: Inter-quartile range, LAN: Light at night, OR: Odds Ratio, Q: Quartile, T: Tertile, VIIRS: Visible Infrared Imaging Radiometer Suite, * : HR for cohort studies and OR for case-control studies

Annex 4: Estimation of minimum detectable ORs for CECILE Study, E3N-Generations Cohort and the C3-Nuit study.

Minimum detectable odds ratio (OR) is the smallest effect that if true, has an X percent chance of producing an impact estimate at a Y level of significance, where X is the statistical power and Y is the level of statistical significance ²⁸⁹.

The prevalence of outdoor LAN in the general population is expected to be very pervasive. Our study populations are also expected to be very high and almost omnipresent in all the study areas. In the CECILE study and in the E3N-Generations cohort, we estimated the ORs using tertiles, quartiles and using per IQR increase in the exposure. Therefore, to estimate the minimum detectable ORs, we considered the highest exposure category as the most exposed group resulting in a prevalence of 25% or 30%.

In the C3-Nuit study, the prevalence of night shift work among controls was 12.5%, which was lower than anticipated, likely due to lower participation rates. Consequently, we also used the national prevalence (16.4%) to estimate the minimum detectable ORs. The sample sizes used estimation were $n_{cases} = 1185$, $n_{controls} = 1282$ in CECILE study, $n_{cases} = 5222$, $n_{controls} = 5222$ in case-controls study nested in E3N-Generations cohort, and $n_{cases} = 671$, $n_{controls} = 1016$ in the C3-Nuit study. For the calculations, parameters were set at 80% for the statistical power and 5% for the type I error probability.

		Minimum detectable ORs		
		CECILE	E3N-Generations	C3-Nuit
Outdoor LAN				
Study prevalence 1	25%	1.28	1.14	-
Study prevalence 2	30%	1.26	1.12	-
Night shift work				
Study prevalence	12.5%	-	-	1.48
National prevalence	16.4%	-	-	1.43

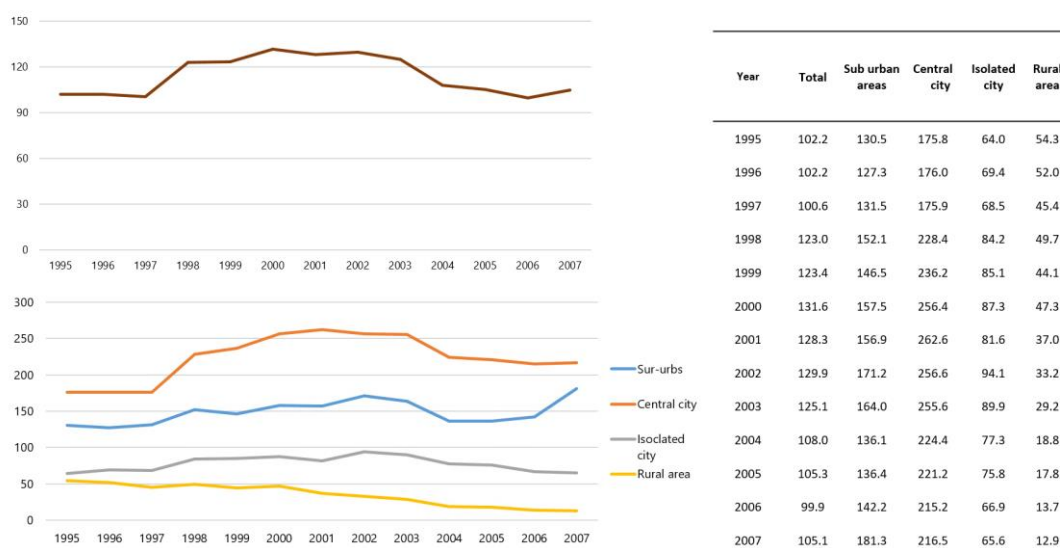
Annex 5: Odds ratios and 95% CI for associations between breast cancer risk and variables considered in the CECILE Study.

	Cases (n=1185)	Controls (n=1282)	OR (95% CI) +
Department, n (%)			
<i>Côte d'Or</i>	369 (31.1)	442 (34.5)	0.87 (0.73-1.02)
<i>Ille-et-Vilaine</i>	816 (68.9)	840 (65.5)	1.16 (0.98-1.37)
Age at reference			
Mean ± SD	55.4 ± 10.6	55.4 ± 11.0	1.00 (0.99-1.01)
Urbanization, n (%)			
Rural areas	325 (27.4)	462 (36.1)	Ref
Non- rural			1.50 (1.27-1.78)
Main cities	393 (33.1)	352 (27.5)	1.59 (1.30-1.94)
Suburbs	211 (17.8)	186 (14.5)	1.62 (1.27-2.06)
Isolated cities	256 (21.6)	280 (21.8)	1.26 (1.00-1.58)
Education level, n (%)			
No school/ Primary	271 (22.9)	298 (23.2)	Ref
Basic Secondary	427 (36.0)	507 (39.6)	0.93 (0.75-1.14)
Secondary	162 (13.7)	187 (14.6)	0.94 (0.72-1.23)
University degree	325 (27.4)	290 (22.6)	1.23 (0.99-1.54)
Age at menarche			
Mean ± SD	12.93 ± 1.6	13.11 ± 1.7	0.94 (0.89-0.98)
Parity, n (%)			
Nulliparous	126 (10.6)	83 (6.5)	Ref
1	182 (15.4)	165 (12.9)	0.73 (0.52-1.04)
2	472 (39.8)	458 (35.7)	0.68 (0.50-0.92)
≥3	405 (34.2)	576 (44.9)	0.45 (0.33-0.61)
Age at 1st full-term pregnancy ^a, n (%)			
<21 yrs	262 (24.7)	347 (28.9)	Ref
22-24 yrs	306 (28.9)	381 (31.8)	1.05 (0.85-1.31)
25-27 yrs	232 (21.9)	279 (23.3)	1.09 (0.86-1.38)
≥28 yrs	259 (24.6)	192 (16.0)	1.79 (1.40-2.29)
Menopausal status, n (%)			
Pre-menopausal	468 (39.5)	480 (37.4)	Ref
Post-menopausal	717 (60.5)	802 (62.6)	0.91 (0.77-1.07)
BMI (kg/m²)			
18.5	41 (3.5)	34 (2.6)	Ref
18.5–25	684 (57.7)	708 (55.2)	0.80 (0.50-1.27)
<25.0	460 (38.8)	540 (42.1)	0.70 (0.43-1.12)
Menopausal hormonal therapy ^b, n (%)			
Never	355 (49.5)	388 (48.4)	Ref
Current	146 (20.4)	121 (15.1)	1.24 (0.96-1.61)
Former	216 (30.1)	293 (36.5)	0.78 (0.64-0.96)
Oral contraceptives use, n (%)			
Never	648 (56.7)	738 (57.6)	Ref
Former users	140 (11.8)	137 (10.7)	1.16 (0.88-1.52)
Current users	397 (33.5)	407 (31.7)	1.10 (0.91-1.34)

	Cases (n=1185)	Controls (n=1282)	OR (95% CI) †
Breast cancer among 1st degree relatives, n (%)			
Yes	204 (17.2)	139 (10.8)	1.71 (1.36-2.16)
No	981 (82.8)	1143 (89.2)	Ref
Alcohol consumption, n (%)			
0-3 glasses per week	923 (77.9)	1065 (83.1)	Ref
4-7 glasses per week	151 (12.7)	183 (14.3)	0.85 (0.67-1.08)
>7 glasses per week	111 (9.4)	132 (10.3)	0.87 (0.65-1.12)
Smoking status, n (%)			
Never smokers	728 (61.4)	786 (61.4)	Ref
Former smokers	253 (21.4)	289 (22.6)	0.94 (0.77-1.14)
Current smokers	204 (17.2)	205 (16.0)	1.08 (0.87-1.34)
Night shift work ^c, n (%)			
Never	1073 (90.5)	1171 (91.4)	Ref
Ever	110 (9.5)	110 (8.6)	1.13 (0.86-1.49)
Air pollution (mean annual exposure during the 10 years before the reference date)			
Nitrogen-dioxide (NO₂ µg/m³)			
Mean ± SD	17.1 ± 6.7	16.2 ± 6.7	1.02 (1.01-1.03)
Particulate matter 2.5 (PM_{2.5} µg/m³)			
Mean ± SD	13.7 ± 1.2	13.5 ± 1.3	1.05 (1.00-1.11)
Particulate matter 10 (PM₁₀ µg/m³)			
Mean ± SD	21.7 ± 1.5	21.5 ± 1.6	1.13 (1.06-1.20)

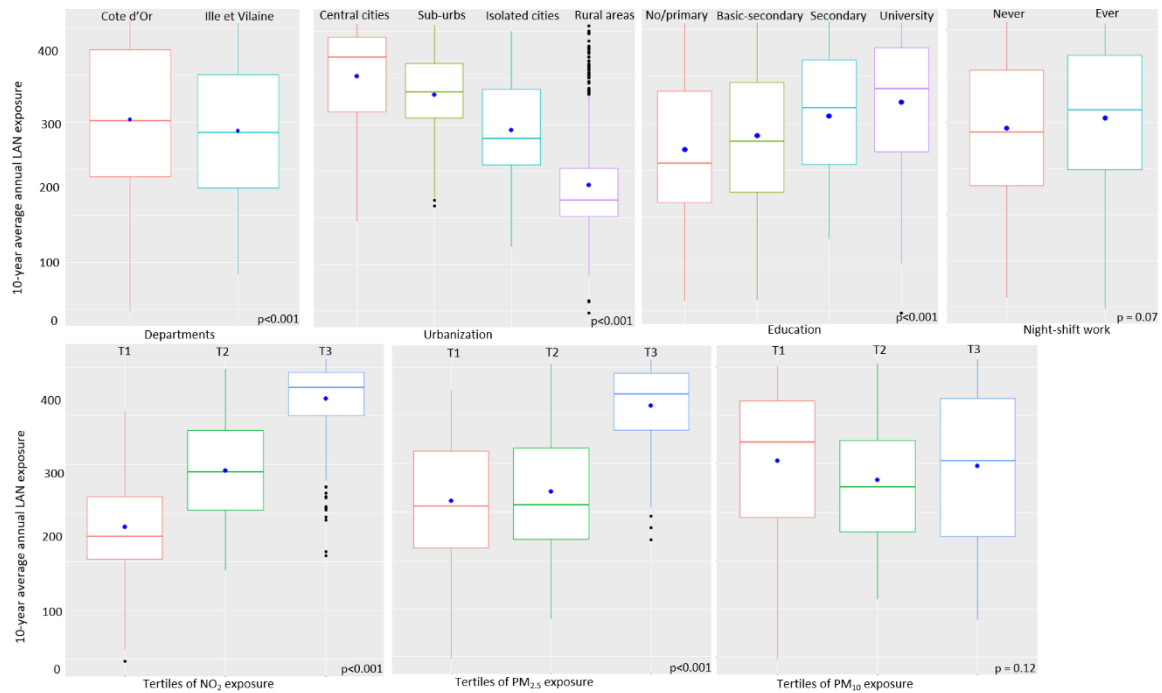
a: parous women only, b: menopausal women only, c: night shift work defined as at least 3 hours between 12-5 a.m. at least in one job during the whole career, BMI: Body-mass Index; LAN: Artificial Light at night, † OR from unconditional logistic regression models adjusted on age at reference and department

Annex 6: Annual average exposure to outdoor LAN (nW/cm²/sr) from 1990-2007 in CECILE Study.

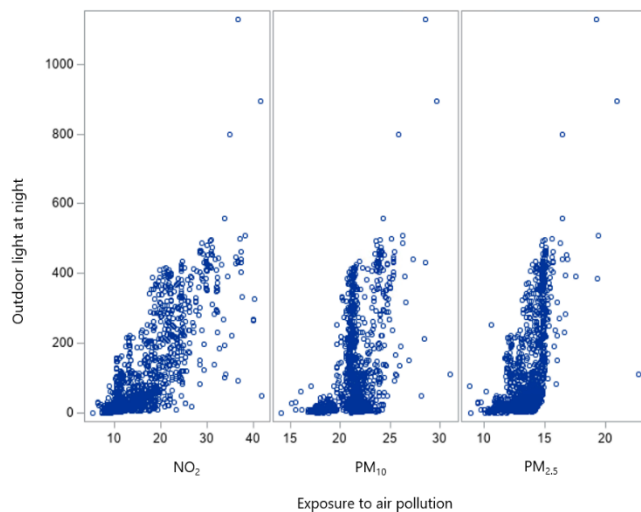


Among controls only (top-left) and by urbanization level (bottom-left)

Annex 7: Distribution of outdoor LAN (logarithmic scale) by departments, urbanization and air pollution exposure among controls only in CECILE study.



Annex 8: Scatter plot (left) and correlation matrix (right) showing Pearson's correlation coefficient and p-values outdoor LAN and air pollutants among controls only in CECILE Study.



	Light at night	NO ₂	PM ₁₀	PM _{2.5}
Light at night	1			
NO ₂	0.79, p < 0.001	1		
PM ₁₀	0.33, p < 0.001	0.50, p < 0.001	1	
PM _{2.5}	0.59, p < 0.001	0.71, p < 0.001	0.67, p < 0.001	1

Annex 9: Results for multicollinearity test using variance inflation factor (VIF) in fully adjusted models in CECILE Study.

Variable	Variance Inflation Factor
Light at night	2.96367
Department	1.29747
Age at reference	2.94273
Urbanization	1.59710
Education	1.38417
Age at first full term pregnancy	1.67129
Parity	1.54095
Menopausal status and menopausal hormone replacement therapy	2.48451
History of breast cancer among 1 st degree relatives	1.00923
Oral contraceptive use	1.21769
Alcohol consumption	1.06007
BMI	1.08782
Tobacco smoking	1.18252
Night shift work	1.03300
Air pollution (NO ₂)	3.31345

Annex 10: Number of cases and controls by reference year in the case-control study nested within the E3N-Generations cohort.

Reference year	Cases	Controls	Total n(%)
1990	74	74	148 (1.5)
1991	184	184	368 (3.5)
1992	193	193	386 (3.7)
1993	178	178	356 (3.4)
1994	208	208	416 (4.0)
1995	200	200	400 (3.8)
1996	246	246	492 (4.7)
1997	262	262	524 (2.6)
1998	234	234	468 (2.3)
1999	325	325	650 (6.2)
2000	288	288	576 (5.5)
2001	298	298	596 (5.7)
2002	322	322	644 (6.2)
2003	301	301	602 (5.8)
2004	297	297	594 (5.7)
2005	253	253	506 (5.8)
2006	258	258	516 (4.7)
2007	269	269	538 (5.2)
2008	238	238	476 (4.6)
2009	202	202	404 (3.9)
2010	185	185	370 (3.5)
2011	207	207	414 (4.0)

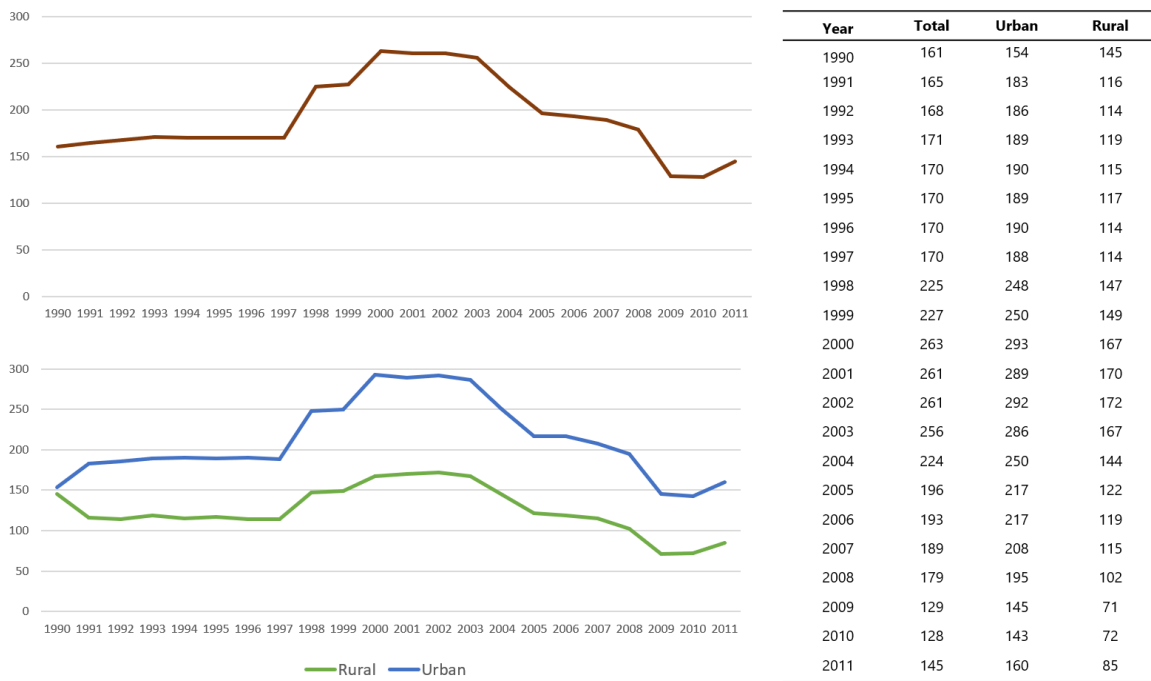
Annex 11: Odds ratios and 95% CI for associations between breast cancer risk and variables considered in the case-control study nested within the E3N-Generations cohort.

	Cases n=5222	Controls n=5222	OR (95% CI)
Age at diagnosis (yrs)			
Mean ± SD	60.6 ± 8.1	60.6 ± 8.1	1.11 (1.02-1.21)
Education level, n(%)			
≤Secondary education	802 (15.4)	874 (16.7)	Ref
1-2 year university degree	2497 (47.8)	2621 (50.2)	1.05 (0.94-1.17)
≥3 year university degree	1923 (36.8)	1727 (33.1)	1.23 (1.10-1.39)
History of breast cancer among 1st degree relatives, n(%)			
No	4336 (83.0)	4997 (89.4)	Ref
Yes	886 (17.0)	555 (10.6)	1.74 (1.55-1.95)
Personal history of benign breast disease, n(%)			
Never	3688 (70.6)	4045 (77.5)	Ref
Ever	1534 (29.4)	1177 (22.5)	1.45 (1.33-1.59)
Age at menarche			
Mean ± SD	12.8 ± 1.4	12.8 ± 1.4	0.98 (0.95-1.01)
In categories, n(%)			
<12 years	1098 (21.0)	1050 (20.1)	Ref
12-14 years	2704 (51.8)	2702 (51.7)	0.95 (0.83-1.09)
≥14 years	1420 (27.2)	1470 (28.2)	0.83 (0.69-1.00)
Parity n(%)			
Nulliparous	674 (12.9)	562 (10.8)	1.40 (1.22-1.60)
1 or 2	3198 (61.2)	3101 (59.4)	1.20 (1.10-1.32)
≥3	1350 (25.9)	1559 (29.8)	Ref
Age at first full-term pregnancy ^a			
<30 yrs	3867 (85.0)	4101 (88.0)	Ref
≥30 yrs	681 (15.0)	559 (12.0)	1.36 (1.19-1.54)
Breastfeeding at least 1 child, n(%) ^a			
Never	1709 (37.6)	1811 (38.9)	Ref
Ever	2839 (62.4)	2849 (61.1)	1.06 (0.97-1.15)
Oral contraceptive use, n(%)			
Never	2147 (41.1)	2158 (41.3)	Ref
Ever	3075 (58.9)	3064 (58.7)	1.01 (0.93-1.10)
Menopausal status, n(%)			
Pre-menopausal	874 (16.7)	806 (15.4)	Ref
Post-menopausal	4348 (83.3)	4416 (84.6)	0.76 (0.64-0.91)
Menopausal hormonal therapy, n(%) ^b			
No	1177 (27.1)	1390 (31.5)	Ref
Yes	3062 (70.4)	2912 (65.9)	0.71 (0.64-0.79)
Missing	109 (2.5)	114 (2.6)	

	Cases n=5222	Controls n=5222	OR (95% CI)
BMI, n(%)			
<18.5 kg/m ²	142 (2.7)	157 (3.0)	Ref
18.5 – 24.9 kg/m ²	3553 (68.0)	3640 (69.7)	0.96 (0.85-1.07)
25-29.9 kg/m ²	1210 (23.2)	1106 (21.2)	0.88 (0.69-1.13)
≥30 kg/m ²	317 (6.1)	319 (6.1)	
Alcohol consumption, n(%)			
Never	1116 (21.4)	1197 (22.9)	Ref
>0-10 grams per day	1608 (30.8)	1640 (31.4)	1.09 (0.93-1.27)
>10 grams per day	1502 (28.7)	1359 (11.5)	1.26 (1.09-1.46)
Missing	996 (19.1)	1026 (19.7)	
Smoking, n(%)			
Non-smokers	2489 (47.7)	2543 (48.7)	Ref
Current smokers	441 (8.4)	444 (8.5)	1.08 (0.96-1.21)
Former smokers	1755 (33.6)	1688 (32.3)	1.04 (0.95-1.13)
Missing	537 (10.3)	547 (10.5)	
Urbanization, n(%)			
Rural	346 (16.2)	922 (17.7)	Ref
Urban	4376 (83.8)	4300 (82.8)	1.12 (1.01-1.25)
NDVI within 300 m buffer			
Mean ± SD	0.51 ± 0.15	0.52 ± 0.15	0.68 (0.52-0.92)
Urbanization and NDVI			
Urban with low greenness	2627 (50.3)	2505 (48.0)	Ref
Urban with high greenness	1749 (33.5)	1795 (33.5)	0.88 (0.80-0.97)
Air pollution			
NO₂			
Mean ± SD	13.5 ± 11.7	13.3 ± 11.5	1.01 (1.00-1.01)
<Median (10.3 µg/m ³)	2555 (48.9)	2611 (50.0)	Ref
≥Median (10.3 µg/m ³)	2667 (51.1)	2611 (50.0)	1.14 (1.00-1.31)
PM_{2.5}			
Mean ± SD	10.6 ± 7.4	10.5 ± 7.4	1.02 (1.00-1.05)
<Median (9.6 µg/m ³)	2614 (50.1)	2611 (50.0)	Ref
≥Median (9.6 µg/m ³)	2608 (49.9)	2611 (50.0)	0.98 (0.78-1.24)
PM₁₀			
Mean ± SD	14.9 ± 10.2	14.8 ± 10.2	1.01 (1.00-1.03)
<Median (13.5 µg/m ³)	2599 (49.8)	2612 (50.0)	Ref
≥Median (13.5 µg/m ³)	2623 (50.2)	2610 (50.0)	1.10 (0.87-1.40)

BMI: Body-Mass Index, NDVI: Normalized Difference Vegetation Index, NO₂: Nitrogen dioxide, PM: Particulate matter

Annex 12: Line charts showing the annual average LAN exposure (nW/cm²/sr) in the case-control study nested within the E3N-Generations cohort.



Among controls only (top-left) and by urban-rural status (bottom-left)

Annex 13: Distribution of exposure to outdoor LAN (at reference) among controls by variables of interest in the case-control study nested within the E3N-Generations cohort.

	Mean ± SD	Median (Q1- Q3)	Min-Max	p-values [†]
Menopausal status				
Pre-menopausal	179.5 ± 222.7	94.7 (25.3-246.2)	0.0-1420.4	0.006
Post-menopausal	202.8 ± 239.6	114.2 (12.6-297.4)	0.0-2021.6	
Urbanization				
Rural	140.9 ± 189.9	63.0 (16.8-199.7)	0.0-1707.6	<.0001
Urban	219.9 ± 247.9	130.1 (36.8-324.3)	0.0-2021.6	
Education level at recruitment				
≤Secondary education	179.7 ± 211.7	96.8 (26.8-271.2)	0.0-1472.2	<.0001
1-2 year university degree	161.2 ± 197.1	83.0 (22.8-233.3)	0.0-1408.7	
≥3 year university degree	266.7 ± 285.6	181.7 (51.9-375.9)	0.0-2021.6	
Air pollution: NO₂ (µg/m³)				
<Median (10.3 µg/m ³)	136.8 ± 64.54	57.9 (17.1-185.7)	0.0-2021.6	<.0001
≥Median (10.3 µg/m ³)	261.6 ± 261.4	189.1 (63.5-376.2)	0.0-1880.2	
Air pollution: PM_{2.5} (µg/m³)				
<Median (9.6 µg/m ³)	172.9 ± 222.4	86.9 (22.0-243.7)	0.0-2021.6	<.0001
≥Median (9.6 µg/m ³)	225.5 ± 248.4	139.3 (42.1-330.9)	0.0-1880.2	
Air pollution: PM₁₀ (µg/m³)				
<Median (13.5 µg/m ³)	173.6 ± 219.8	90.2 (23.2-248.1)	0.0-2021.6	<.0001
≥Median (13.5 µg/m ³)	224.8 ± 250.9	134.8 (39.4-330.4)	0.0-1880.2	

[†] :p- values derived from Wilcoxon signed rank test for variables with 2 categories and Kruskal Wallis test for variables with >2 categories

Annex 14: Odds ratio and 95% confidence intervals for the association between outdoor LAN and breast cancer risk adjusting for air pollution (particulate matter) in the case-control study nested within the E3N-Generations cohort.

Outdoor LAN (nW/cm ² /sr)	Cases, n (%)	Controls, n (%)	Model 1	Model 2	Model 3c: Model 2+PM _{2.5}	Model 3d: Model 2+PM ₁₀
			OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Q1 (0-29.5)	1038 (22.6)	1306 (25.0)	Ref	Ref	Ref	Ref
Q2 (29.6-110.3)	1298 (24.9)	1305 (25.0)	1.09 (0.97-1.22)	1.07 (0.95-1.20)	1.07 (0.95-1.20)	1.07 (0.95-1.20)
Q3 (110.4-290.7)	1341 (25.7)	1306 (25.0)	1.14 (1.02-1.28)	1.11 (0.99-1.25)	1.11 (0.98-1.25)	1.11 (0.98-1.25)
Q4 (290.8-2021.6)	1375 (26.3)	1305 (25.0)	1.20 (1.06-1.37)	1.13 (0.99-1.29)	1.12 (0.96-1.30)	1.12 (0.97-1.29)
Per IQR increase^e	5222	5222	1.12 (1.06-1.18)	1.09 (1.03-1.15)	1.10 (1.03-1.17)	1.10 (1.03-1.17)

LAN: Light at night, IQR: Inter-quartile range (261.26 nW/cm²/sr based on the distribution of LAN among controls only). NO₂: nitrogen dioxide, PM: particulate matter

Model 1: adjusted for age at diagnosis

Model 2: further adjustment on reproductive and hormonal factors (parity, age at first full-term pregnancy, breastfeeding, oral contraceptive use, history of breast cancer among 1st-degree relatives, menopausal status at diagnosis, and menopausal hormonal therapy use), lifestyle-related factors at diagnosis (BMI, smoking and alcohol consumption), and education

Model 3: Model 2 + further adjustment on air pollution (PM_{2.5} or PM₁₀)

Annex 15: Odds ratio and 95% confidence intervals for the association between residential greenness (NDVI in 300 m buffer) and breast cancer risk adjusting for different covariates in the case-control study nested within the E3N-Generations cohort.

Greenness (NDVI)	Cases, n (%)	Controls, n (%)	Model 1	Model 2
			OR (95% CI)	OR (95% CI)
Q1 (0.08-0.42)	1407 (26.9)	1305 (25.0)	Ref	Ref
Q2 (0.43-0.53)	1321 (25.3)	1306 (25.0)	0.92 (0.83-1.03)	0.96 (0.85-1.07)
Q3 (0.54-0.64)	1204 (25.1)	1306 (25.0)	0.84 (0.74-0.94)	0.88 (0.78-0.99)
Q4 (0.64-0.86)	1290 (24.7)	1305 (25.0)	0.89 (0.79-1.01)	0.95 (0.84-1.07)
Per IQR increase	5222	5222	0.92 (0.87-0.98)	0.95 (0.89-1.02)

IQR= 0.22 based on the distribution of NDVI among controls only, NDVI: Normalized Difference Vegetation Index

All estimates are from conditional logistic regression models adjusted in the following order:

Model 1: adjusted for age at diagnosis

Model 2: further adjustment on reproductive and hormonal factors (parity, age at first full-term pregnancy, breastfeeding, oral contraceptive use, history of breast cancer among 1st-degree relatives, menopausal status at reference and menopausal hormonal therapy use), lifestyle-related factors at reference (BMI, smoking and alcohol consumption), and education

Annex 16: Correlation matrix (Pearson correlation coefficient and p-values) for outdoor LAN, air pollution, and residential greenness among controls only in the case-control study nested within the E3N-Generations cohort.

	LAN	NO₂	PM_{2.5}	PM₁₀	NDVI
LAN	1.00				
NO₂	0.46, p <.0001	1.00			
PM_{2.5}	0.19, p <.0001	0.89, p <.0001	1.00		
PM₁₀	0.21, p <.0001	0.87, p <.0001	0.98, p <.0001	1.00	
NDVI	-0.66, p <.0001	-0.35, p <.0001	-0.16, p <.0001	-0.18, p <.0001	1.00

LAN: Light at night, NDVI: Normalized Difference Vegetation Index, NO₂: Nitrogen dioxide, PM: Particulate matter

Annex 17: Results for multicollinearity test using variance inflation factor (VIF) in fully adjusted models in the case-control study nested within the E3N-Generations cohort.

Variables	Variance Inflation
Light at night	2.15252
Age at diagnosis	2.77472
Age at inclusion	4.04924
Department	1.10506
Menopausal status at inclusion	2.45671
Education	1.09395
Parity	1.13687
Menopausal status +menopausal hormonal therapy	1.44693
History of BC in 1 st relatives	1.00397
Oral contraceptive use	1.24825
Breastfeeding	1.14042
BMI at reference	1.04044
Alcohol consumption at reference	1.92372
Smoking at reference	1.52777
NO ₂ at reference	1.32873
NDVI 300m at reference	1.86843

Questionnaire C3-Nuit

Introduction

Bonjour,

Je suis [nom enquêteur] de la société Cemka-Eval. Je travaille pour le Centre de recherche en Epidémiologie et Santé des Populations (CESP) et la cohorte Constances de l'INSERM. Pourrais-je parler à [M./Mme Prénom Nom] s'il vous plaît ?

Enquêteur, si besoin précisez : "Nous réalisons actuellement une étude auprès des volontaires de la cohorte Constances sur les horaires de travail de nuit, les troubles du sommeil et leurs effets sur la santé. [M./Mme Prénom Nom] a été sélectionné pour participer à cette recherche."

Une fois la bonne personne en ligne :

Bonjour,

Je suis [nom enquêteur] de la société Cemka-Eval. Je travaille pour le Centre de recherche en Epidémiologie et Santé des Populations (CESP) et la cohorte Constances de l'INSERM.

Nous réalisons actuellement une étude auprès des volontaires de la cohorte Constances sur le travail de nuit, les troubles du sommeil et leurs effets sur la santé. Vous avez été sélectionné(e) parmi les volontaires de la cohorte Constances. Nous souhaiterions que vous acceptiez de répondre à un questionnaire d'environ [à adapter selon estimation nb emplois déjà complétés] minutes.

Acceptez-vous de participer à cette étude ?

1. Oui, tout de suite
2. Oui, plus tard → prise de rendez-vous
3. Non -> Codes de chutes

Enquêteur : Si remarque de l'interviewé sur la réalisation de l'étude en temps de COVID-19

« Cette étude a démarré il y a plus d'un an et l'organisation de cette étude nous amène à poursuivre les interviews en ce temps d'épidémie. »

Enquêteur : si besoin, précisez

« Votre participation est essentielle pour la qualité scientifique de l'étude. Les résultats de cette étude seront utilisés pour mieux adapter les horaires de travail dans certains secteurs d'activité, et prévenir l'apparition de maladies.

Les réponses que vous apporterez à ce questionnaire resteront strictement confidentielles. Les données recueillies feront l'objet uniquement de traitement statistique.

Cette recherche a reçu l'autorisation de la CNIL (Commission Nationale de l'Informatique et des Libertés) et l'avis favorable du Comité de Protection des Personnes (CPP).

Une lettre de présentation de l'étude vous a été adressée [voir date envoi lettre]. »

Partie 1 : Historique de carrière

Q1. Pour commencer, je vais citer les informations sur vos emplois que vous avez renseignées lors de votre inclusion dans la cohorte Constances, en [date inclusion mois/année].

Vous avez renseigné [nb_emploi] emploi(s) de plus de 6 mois

Si a renseigné une date de retraite, afficher :

Q1b. Vous avez précisé être en retraite depuis le : [date retraite]. Est-ce exact ?

1. Oui

2. Non

Si non,

En quelle date avez-vous pris votre retraite ?

/jj / mm / aaaa /

Boucle 1

Si au moins un emploi déjà renseigné

Q2. Pouvez-vous valider les informations suivantes ?

Enquêteur, préciser si besoin : « Ces informations sont celles que vous avez renseignées dans le questionnaire lors de votre inclusion dans la cohorte et qui ont été enregistrées. »

Enquêteur : tous les 3 items, demandez : "Est-ce exact ?" ; corriger directement la réponse.

N° EMPLOI

Q2a. A partir de l'année [année début de l'emploi] **jusqu'à** [année de fin de l'emploi] **En cours**

Q2b. Vous avez exercé la profession de : [Profession exercée emploi (non codée)]

Q2c. Dans/en (production ou secteur d'activité de l'emploi) : [production ou secteur d'activité emploi (non codée)]

Q2d. Vous avez travaillé à [temps plein / temps partiel].

Q2e. Habituellement pour cet emploi, quel était, le nombre moyen d'heures travaillées par semaine (y compris les heures supplémentaires) ?

/_/_/ heures

Q2f. Vous étiez : [Salarié / à votre compte / saisonnier, intérimaire]

Si saisonnier/intérimaire

Q2g. Combien de mois par an exercez-vous cet emploi ? /_/_/ mois par an

Q2h. Vous étiez en : [CDI / CDD / autre en clair]

Q2i. Vous avez interrompu votre travail de [année début] **à** [année fin]

Q2j. Pour raison de [santé / chômage / autre en clair]

Fin boucle 1

Possibilité de supprimer un emploi ou d'ajouter un nouvel emploi.

Si année de retraite renseignée (Q1b) < année diagnostic/référence

→ partie 2 (Horaires)

Nous nous intéressons aux nouveaux emplois depuis votre inclusion dans la cohorte Constances jusqu'à aujourd'hui.

Q3 : Entre votre dernier emploi renseigné et aujourd'hui, avez-vous un nouvel emploi de plus de 6 mois ?

Enquêteur : Rappelez si nécessaire la situation ou l'emploi ainsi que la date de fin

- Oui
- Non

Si "jamais travaillé" est renseigné dans le calendrier professionnel

Q3bis) Depuis votre inclusion dans la cohorte en [date inclusion], avez-vous exercé un emploi de plus de 6 mois ?

- 1) Oui
- 2) Non

Boucle 2

Si nouvel emploi (Q3=1 ou Q3bis =1)

Q4. Nouvelle fiche emploi à compléter

Q4a. En quelle année avez-vous débuté votre nouvel emploi ? /___/

Q4b. Quelle profession avez-vous exercé ? /_____/

Q4c. Dans quel secteur d'activité ou de production ? / _____ /

Q4d. Etiez-vous à temps plein ou à temps partiel ? 1. Temps plein 2. Temps partiel

Q4e. Quel était le nombre d'heures travaillées par semaine (y compris les heures supplémentaires) ?
 /_/_/ heures

Q4f. Etiez-vous salarié, à votre compte ou saisonnier/intérimaire ?
 1. salarié
 2. à votre compte 3. saisonnier/intérimaire
Si saisonnier/intérimaire

Q4g. Combien de mois par an exercez-vous cet emploi ? /_/_/ mois par an

Q4h. Vous étiez en : CDI / CDD / Autre en clair

Q4i. Avez-vous interrompu votre travail pendant plus de 6 mois ?
 - Oui
 - Non

Si Q4i=1 (oui)

Q4j. Pendant quelle(s) année(s) avez-vous interrompu votre travail ?
 De /_/_/ à /_/_/

Si Q4i=1 (oui)

Q4h. Pour quelle raison avez-vous interrompu votre travail pendant plus de 6 mois ?
 1) Santé
 2) Chômage
 3) Autre (à préciser : / _____ /)

Enquêteur : Les situations professionnelles sont-elles renseignées jusqu'à aujourd'hui ?

- Oui (→ aller partie horaire de travail)
- Non

Si pas de nouvel emploi (Q3_1=NON OU Q3bis=NON)

Fin boucle 2

Q3_3 : Depuis votre dernier emploi renseigné, avez-vous pris votre retraite ?

- Oui
- Non

Q5. Quelle est la date de votre départ à la retraite ?

Enquêteur : format mm/aaaa

/_/_/_____/

Si aucun emploi exercé de plus de 6 mois (Q1a=0 emploi et Q3bis=non), passer à la partie « Sommeil ».

Partie 2 : HORAIRES DE TRAVAIL

Affichage de la liste des emplois validés

Présenter l'année de début, puis l'année de fin et le libellé de l'emploi.

Pour renseigner les horaires de travail au cours de votre vie, nous allons maintenant passer en revue chacun des emplois que vous avez eus.

Enquêteur : sélectionner l'emploi du plus ancien au plus récent

Boucle 3

Concernant votre emploi de [profession exercée emploi n°X] [secteur d'activité emploi n°X] **exercé de** [année début] à [année de fin].

Boucle 4

Type d'horaire

G1. LORSQUE VOUS AVEZ DEBUTE DANS CET EMPLOI EN [année début de l'emploi sélectionné] **vous aviez des horaires...**

(G1 bis passage suivant) : **LORSQUE VOUS AVEZ CHANGE D'HORAIRE DANS CET EMPLOI à partir de** [année débutG7a] **vous aviez des horaires...**

Enquêteur : au premier passage, lire les modalités en entier puis aux passages suivants citer uniquement "vous aviez des horaires alternants, irréguliers ou fixes ?"

1. ...**alternants**, c'est-à-dire que vous travailliez dans des équipes ("brigades" ou par "quarts") dont les horaires tournaient selon un rythme régulier par exemple en 3X8, 2X8, 2X12...
2. ...**fixes**, c'est-à-dire vous aviez des mêmes horaires de travail qui variaient peu d'un jour à l'autre ou d'une semaine à l'autre
3. ...**irréguliers**, c'est-à-dire vous n'aviez ni horaires fixes, ni alternants et pouvaient varier d'un jour à l'autre ou d'une semaine à l'autre

Passation dans un des trois blocs selon réponse G1/G1bis

BLOC « horaires FIXES » :

Pour rappel : Emploi de [profession exercée emploi n°X] [secteur d'activité emploi n°X] **exercé à partir de** [année début] [ou année de modification d'horaire G7a] – **Horaire FIXE**

F1. En général, à quelle heure commencez-vous votre travail ?

/__/_/h/___/min

F2. En général, à quelle heure finissez-vous votre travail ?

/__/_/h/___/min

F3. En moyenne, combien de jours/nuits travaillez-vous par semaine ?

semaine

OU mois

/__/_/ jours/nuits travaillé(e)s en moyenne

Commentaires éventuels /_____/ (à afficher en bas de chacune des pages)

F5a. Vous arrivait-il de travailler, tôt le matin c'est-à-dire avant 7 du matin, tard le soir après 21 H ou de nuit entre minuit et 5 heures du matin (en dehors des horaires fixes que vous venez de préciser) ?

1. Oui

2. Non

Si oui en F5a,

F5b. Combien de fois par mois ou par an cela vous arrivait-il ?

/___/ par mois

OU /___/ par an

Si oui en F5a,

F5c. A quelles heures commenciez-vous et finissiez-vous ?

De /__/_/h/__/min à /__/_/h/__/min

BLOC « horaires ALTERNANTS »

Pour rappel : Emploi de [profession exercée emploi n°X] [secteur d'activité emploi n°X] **exercé à partir de** [année début] [ou année de modification d'horaire] – **Horaires ALTERNANTS**

R1. Vous avez travaillé en équipes à horaires alternants. Quel était le type d'horaire alternant ? Par exemple « 3 x 8 » pour indiquer qu'il y avait 3 équipes de 8 heures chacune.

1. En 3 x 8 (*trois huit*)
2. En 2 x 8 (*deux huit*)
3. En 2 x 12 (*deux douze*)
4. Autre, précisez :

Lequel ? Précisez le nombre d'équipes X nombre d'heures /___ x ___/

R2. Quel était le rythme de rotation, c'est-à-dire, au bout de combien de jours, semaines ou mois votre planning revenait-il à sa configuration initiale ?

Enquêteur : préciser si besoin : "par exemple, pour un travail en 3 x 8 avec une rotation toutes les semaines, le planning revenait à sa configuration initiale au bout de 3 semaines."

/___/ jours
OU /___/ semaines
OU /___/ mois

« Le MATIN »

R3. Lorsque vous étiez du matin, à quelle heure commenciez-vous votre travail ?

/__/_/h/__/min (ne travaillait pas le matin)

Si travaillait le matin

R3a. A quelle heure finissiez-vous ?

/__/_/h/__/min

R3b. Lorsque vous étiez du matin, quel était en moyenne le nombre de matins de travail par semaine ?

Enquêteur : relancer "Pendant vos périodes où vous étiez du matin"

/___/ matins travaillés en moyenne par semaine (sur des périodes de travail du matin)
(possibilité de répondre par mois)

R3d. Lorsque vous étiez du matin, combien de jours de repos aviez-vous par semaine ?

/___/ jours de repos

« L' APRES-MIDI »

R4. Lorsque vous étiez d'après-midi, à quelle heure commenciez-vous votre travail ?

/__/_/h/__/min

(Ne travaillait pas l'après-midi)

Si travaillait l'après-midi

R4a. A quelle heure finissiez-vous ?

/_/_/h/_/_/min

R4b. Lorsque vous étiez d'après-midi, quel était en moyenne le nombre d'après-midi de travail par semaine ?

/_/_/ après-midi travaillés en moyenne par semaine (sur des périodes de travail d'après-midi)
(possibilité de répondre par mois)

R4d. Lorsque vous étiez d'après-midi, combien de jours de repos aviez-vous par semaine ?

/_/_/ jours de repos

« La NUIT »

R5. Lorsque vous étiez de nuit, à quelle heure commenciez-vous votre travail ?

/_/_/h/_/_/min

(Ne travaillait pas la nuit)

Si travaillait la nuit

R5a. A quelle heure finissiez-vous ?

/_/_/h/_/_/min

R5b. Lorsque vous étiez de nuit, quel était en moyenne le nombre de nuits de travail par semaine ?

/_/_/ nuits travaillées en moyenne par semaine (sur des périodes de travail d'après-midi)
(possibilité de répondre par mois)

R5c. En moyenne, combien de nuits successives, sans interruption par des jours de repos, travailliez-vous ?

/_/_/ nuits successives

R5d. Lorsque vous étiez de nuit, combien de jours de repos aviez-vous par semaine ?

/_/_/ jours de repos

R5e. Après le dernier poste de nuit, vous passiez à l'équipe ...

- du matin
- d'après-midi
- (indifféremment l'un ou l'autre)

BLOC « horaires IRREGULIERS »

Pour rappel : Emploi de [profession exercée emploi n°X] [secteur d'activité emploi n°X] **exercé à partir de** [année début] [ou année de modification d'horaire] – **Horaires IRREGULIERS**

I1. Vous arrivait-il de commencer à travailler tôt le matin, c'est-à-dire avant 7h du matin ?

1. Oui
2. Non

Si oui en I1,

I1a. Lorsque vous commencez à travailler tôt le matin, le plus souvent, vers quelle heure commencez-vous votre travail ?

/_/_/h /_/_/min

Si oui en I1,

I1b. Le plus souvent, vers quelle heure finissiez-vous votre travail ?

/_/_/h /_/_/min

Commentaires éventuels : /_____/

I1c. Lorsque vous commencez à travailler tôt le matin, cela arrivait en général en moyenne sur une année...

1. une ou plusieurs fois par semaine
2. une ou plusieurs fois par mois (moins d'une fois par semaine mais plus d'une fois par mois)
3. moins d'une fois par mois

I2. Vous arrivait-il de finir votre travail tard le soir, c'est-à-dire après 21h ?

1. Oui
2. Non

Si oui en I2,

I2a. Lorsque vous finissiez de travailler tard le soir, le plus souvent, vers quelle heure finissiez-vous votre travail ?

/_/_/h /_/_/min

I2b. Le plus souvent, vers quelle heure commencez-vous votre travail ?

/_/_/h /_/_/min

Commentaires éventuels : /_____/

I2c. Lorsque vous finissiez de travailler tard le soir, cela arrivait en moyenne sur une année...

1. une ou plusieurs fois par semaine
2. une ou plusieurs fois par mois (moins d'une fois par semaine mais plus d'une fois par mois)
3. moins d'une fois par mois

I3. Vous arrivait-il de travailler la nuit, c'est-à-dire au moins trois heures entre minuit et 5h du matin ?

1. Oui
2. Non

Si oui en I3,

I3a. Lorsque vous avez travaillé de nuit, le plus souvent, vers quelle heure commencez-vous votre travail?

/_/_/h /_/_/min

Commentaires éventuels : /_____/

I3b. Le plus souvent, vers quelle heure finissiez-vous votre travail?

/_/_/h /_/_/min

Commentaires éventuels : /_____/

I3c. Lorsque vous avez travaillé de nuit, cela arrivait en moyenne sur une année...

1. une ou plusieurs fois par semaine
2. une ou plusieurs fois par mois (moins d'une fois par semaine mais plus d'une fois par mois)
3. moins d'une fois par mois

I4. Vous arrivait-il de travailler en journée entre 7h au plus tôt et 21h au plus tard ?

1. Oui
2. Non

Si oui en I4,

I4a Lorsque vous avez travaillé en journée, le plus souvent, vers quelle heure commencez-vous votre travail ?

/_/_/h /_/_/min

I4b. Le plus souvent, vers quelle heure finissiez-vous votre travail ?

/_/_/h /_/_/min

Commentaires éventuels : /_____/

I4c. Lorsque vous avez travaillé en journée, cela arrivait en moyenne sur une année...

4. une ou plusieurs fois par semaine
5. moins d'une fois par semaine mais plus d'une fois par mois
6. moins d'une fois par mois

Retour questions générales "type horaire" et validation période-emploi

G2. Travaillez-vous les dimanches et les jours fériés ?

1. Jamais ou rarement
2. Une à deux fois par mois
3. Toujours ou presque

G3. Travaillez-vous les samedis ?

1. Jamais ou rarement
2. Une à deux fois par mois
3. Toujours ou presque

G4. Quelle était la durée moyenne de votre trajet aller domicile - travail ? (aller simple)

/_/_/h/_/_/min

G5. Au cours de cet emploi, vos horaires de travail ont-ils changé de façon notable ?

Enquêteur : Si besoin, relancer par "Avez-vous modifié votre type d'horaire de travail (en horaire alternant, irrégulier ou fixe) ou avez-vous décalé d'au moins 4 heures vos horaires ?"

1. Oui
2. Non

Si oui en G7,

G7a. En quelle année vos horaires de travail ont-ils changé ?

En / ____/

--> Si G7=1 (changement d'horaires), aller en G1

--> Si G7=2 (A eu les mêmes horaires tout au long de l'exercice), fin boucle 4, aller à l'introduction, emploi suivant.

Fin boucle 4

→ Si pas d'autre emploi, aller en partie 3 "sommeil"

Fin boucle 3

Partie 3 : SOMMEIL

Nous allons maintenant parler de vos habitudes de vie, de sommeil et de repas.

S1 Si vous étiez absolument libre de vous coucher à l'heure que vous vouliez, sans obligation le lendemain, à quelle heure vous coucheriez-vous ?

Vous vous coucheriez à : /__ / h /__ / min

S2 Si vous étiez absolument libre de vous lever à l'heure que vous vouliez, à quelle heure vous lèveriez-vous ?

Vous vous lèveriez à : /__ / h /__ / min

S3 Pensez-vous être une personne :

- Tout à fait du matin
- Plutôt du matin
- Plutôt du soir
- Tout à fait du soir
- Ni du matin, ni du soir
- (Les 2 : du matin et du soir)
- (Vous ne savez pas)

Si JAMAIS TRAVAILLE

Si "n'a jamais travaillé"

Je vais vous poser des questions sur vos horaires de sommeil et de repas.

Pouvez-vous essayer de vous rappeler des horaires de sommeil et de repas que vous aviez l'année avant votre inclusion dans la cohorte Constances, soit en [année inclusion - 1] ?

Rappelez-vous votre environnement de vie l'année [année d'inclusion -1], soit il y a [=année actuelle-année d'inclusion -1] an(s)

Afficher "N'a pas exercé d'emploi en [année inclusion -1]" --> passer en S4b

SI EN RETRAITE

si "année inclusion-1" >= à date de retraite

Je vais vous poser des questions sur vos horaires de sommeil et de repas.

Afficher " En retraite depuis [année retraite]."

Affichage du tableau des emplois validés. L'enquêteur devra valider auprès de la personne interviewée la situation **du dernier emploi exercé avant la retraite.**

Avant votre retraite, vous avez exercé la profession (...) en /__ [saisir l'année du dernier emploi exercé]/.

Pouvez-vous essayer de vous rappeler des horaires de sommeil et de repas que vous aviez en [année du dernier emploi exercé] ?

Rappelez-vous votre environnement de vie l'année [année du dernier emploi exercé], soit il y a [=année actuelle - année du dernier emploi exercé] an(s)

--> passer en S4a

Sinon,

**Je vais vous poser des questions sur vos horaires de sommeil et de repas.
Pouvez-vous essayer de vous rappeler des horaires de sommeil et de repas que vous aviez l'année
avant votre inclusion dans la cohorte Constances, soit en [année inclusion - 1] ?**

Affichage du tableau des emplois validés. L'enquêteur devra valider auprès de la personne interviewée la situation à l'année "inclusion-1":

"**En [année inclusion -1] vous exerciez la profession (...)**" ; correspondant à un emploi avec ou non une interruption de travail.

ou

"**En [année inclusion -1] vous exerciez la profession (...) et la profession (...)**". Privilégier l'emploi où il exerçait un travail de nuit, sinon, prendre celui exercé le plus longtemps au cours de l'année.

ou

"**En [année inclusion -1] vous ne travaillez pas (interruption de travail)**

Avant votre interruption de travail, vous avez exercé la profession (....) en /__ [saisir l'année de l'emploi précédent l'interruption]/.

--> passer en S4a

Rappelez-vous votre environnement de vie l'année [année d'inclusion -1 OU année de l'emploi précédent l'interruption], soit il y a [=année actuelle-(année d'inclusion -1) OU année de l'emploi précédent l'interruption] an(s)

A tous,

Enquêteur :

laisser le temps à l'interviewé de se remémorer son environnement de vie.

rappeler l'emploi en vous référent au calendrier professionnel ; si travaillait en horaire de jour et de nuit, privilégiez les horaires de nuits. Si horaires alternants ou irréguliers, relancez par "le plus souvent".

Introduction (à répéter): **Lorsque vous travailliez le lendemain,**

S4a En général, à quelle heure vous mettiez-vous au lit ?

/__h/__/min

S5a En général, à quelle heure éteigniez-vous la lumière ?

/__h/__/min

S6a Combien de temps vous fallait-il pour vous endormir ?

/__h/__/min

S7a Lorsque vous travailliez le lendemain, vous arrivait-il de vous réveiller la nuit ?

Enquêteur : si travaillait de nuit, adapter le libellé de la question en précisant "pendant votre période de sommeil" à la place de "la nuit"

Oui

Non

si S7a = OUI

S7a.bis En moyenne, combien de fois vous réveilliez-vous par nuit ?

/__ / fois par nuit

S7a.ter Quelle était la durée totale de ces périodes de réveil par nuit ?

/__ / h/__/min

S8a En général lorsque vous travaillez le lendemain, à quelle heure vous réveilliez-vous définitivement le matin ?

/__ / h / __ / min

S9a Vous arrivait-il de faire la sieste pendant les jours de travail ?

Oui

Non

si S9a = OUI

S9a.bis Combien de fois faisiez-vous la sieste par semaine ?

/__ / fois par semaine

Moins d'une fois par semaine

S9a.ter Quel était le temps moyen d'une sieste ?

/__ / h / __ / min

Enquêteur, à répéter : Les jours de travail.

S10a A quelle heure aviez-vous l'habitude de prendre le petit-déjeuner ?

/__ / h / __ / min

Habituellement ne prend pas de petit-déjeuner

Si ≠ habituellement ne prend pas de petit-déjeuner

S10a.bis. Combien de temps consacriez-vous au petit-déjeuner

/__ / min

S11a A quelle heure aviez-vous l'habitude de prendre le déjeuner ?

/__ / h / __ / min

Habituellement ne prend pas de déjeuner

Si S11a ≠ habituellement ne prend pas de déjeuner

S11a.bis Combien de temps consacriez-vous au déjeuner ?

/__ / min

S12a A quelle heure aviez-vous l'habitude de prendre le dîner ?

/__ / h / __ / min

Habituellement ne prend pas de dîner

Si ≠ habituellement ne prend pas de dîner

S12a.bis Combien de temps consacriez-vous au dîner ?

/__ / min

S13a Aviez-vous l'habitude de grignoter entre les repas ?

Entre le petit-déjeuner et le déjeuner

Entre le déjeuner et le dîner

Entre le dîner et le petit-déjeuner

N'avait pas l'habitude de grignoter

(NSP)

Si en emploi, introduction : Lors de vos périodes de repos ou de vacances en [année d'inclusion -1],

Si pas d'emploi en "année inclusion -1": pas d'introduction.

S4b En général, à quelle heure vous mettiez-vous au lit ?

/__ / h / __ / min

S5b En général, à quelle heure éteigniez-vous la lumière ?

/__ / h / __ / min

S6b Combien de temps vous fallait-il pour vous endormir ?

/__/_/h/__/min

S7b Lors de vos périodes de repos ou de vacances vous arrivait-il de vous réveiller la nuit ?

Oui

Non

si S7 = OUI

S7b.bis En moyenne, combien de fois vous réveilliez-vous par nuit ?

/__/_/ fois par nuit

S7b.ter Quelle était la durée totale de ces périodes de réveil par nuit ?

/__/_/ h/__/min

S8b En général, à quelle heure vous réveilliez-vous définitivement le matin ?

/__/_/ h/__/min

S9b Lors de vos périodes de repos ou de vacances, vous arrivait-il de faire la sieste ?

Oui

Non

si S9b = OUI

S9b.bis Combien de fois faisiez-vous la sieste par semaine ?

/__/_/ fois par semaine

Moins d'une fois par semaine

S9b.ter Quel était le temps moyen d'une sieste ?

/__/_/h/__/min

*Si était en emploi, introduction : enquêteur, répétez : **Lors de vos périodes de repos ou de vacances**,*

S10b

A quelle heure aviez-vous l'habitude de prendre le petit-déjeuner ?

/__/_/h/__/min

Habituellement ne prend pas de petit-déjeuner

Si ≠ habituellement ne prend pas de petit-déjeuner

S10b.bis Combien de temps consacriez-vous au petit-déjeuner ?

/__/_/min

S11b

A quelle heure aviez-vous l'habitude de prendre le déjeuner ?

/__/_/h/__/min

Habituellement ne prend pas de déjeuner

Si S11b ≠ habituellement ne prend pas de déjeuner

S11b.bis Combien de temps consacriez-vous au déjeuner ?

/__/_/min

S12b

A quelle heure aviez-vous l'habitude de prendre le dîner ?

/__/_/h/__/min

Habituellement ne prend pas de dîner

Si S12b ≠ habituellement ne prend pas de dîner

S12b.bis Combien de temps consacriez-vous au dîner ?

/__/_/min

S13b**A visez-vous l'habitude de grignoter entre les repas ?**

- Entre le petit-déjeuner et le déjeuner
- Entre le déjeuner et le dîner
- Entre le dîner et le petit-déjeuner
- N'avait pas l'habitude de grignoter
- (NSP)

A tous,

En [année d'inclusion -1].

S14 En général, vous dormiez dans une chambre...

Enquêteur : si besoin, relancer par « Quelle est votre perception ? »

- Totalemment sombre
- Plutôt sombre
- Plutôt éclairée
- Très éclairée
- (NSP)

si S7a = OUI ou S7b=OUI

S15 Aviez-vous l'habitude d'allumer la lumière quand vous vous réveilliez pendant la nuit ?

- Toujours
- Occasionnellement
- Jamais
- (NSP)

A partir du 15 octobre 2021:

Partie 4 :**Le questionnaire est maintenant terminé.**

Avant de conclure cet entretien, j'aimerais vous demander si vous accepteriez de nous fournir un peu de votre salive. Ce prélèvement réalisé par vous-même, à l'aide d'un kit que nous vous enverrons à domicile, permettra de recueillir une petite quantité de votre ADN.

Cet ADN sera utilisé dans une étude complémentaire qui permettra de savoir si les effets des horaires de travail et de sommeil sur la santé sont influencés par certains gènes qui régulent le rythme veille-sommeil chez tous les individus.

P1. Le kit de prélèvement n'est actuellement plus envoyé systématiquement aux participants. Toutefois, si nous sommes amenés à les envoyer, acceptez-vous de réaliser ce prélèvement ?

Enquêteur, préciser si besoin : "Ce prélèvement est à réaliser à domicile à l'aide d'un kit de prélèvement salivaire accompagné d'un mode d'emploi qui vous seront envoyés par courrier. Il suffit de déposer quelques millilitres de votre salive dans un tube prévu à cet effet. Votre échantillon et votre consentement signé seront à retourner en utilisant les enveloppes pré-affranchies."

Le kit ayant un coût non négligeable pour la recherche, si vous acceptez vous vous engagez à envoyer votre prélèvement.

1. Oui, accepte de réaliser le prélèvement salivaire
2. Non, ne souhaite pas réaliser le prélèvement salivaire

Si oui P1=1,

P2. Nous vous proposons de vous envoyer le kit de prélèvement à l'adresse que vous avez communiqué à l'équipe Constances (adresse à laquelle vous réceptionnez les courriers de Constances). Souhaitez-vous réceptionner le kit de prélèvement à cette adresse ?

- 1) Oui
- 2) Non, souhaite que le kit soit envoyé à une autre adresse

Si non P2=2

P4 Pouvez-vous me préciser votre adresse postale pour l'envoi du kit salivaire ?

!! Coordonnées à saisir dans la base de contact, base de données différente de celle du questionnaire.

.....

Dès que vous aurez reçu le courrier, merci de nous envoyer votre prélèvement et votre consentement signé rapidement.

Votre participation à cette recherche est précieuse. Nous vous remercions d'avoir répondu au questionnaire et de réaliser le prélèvement salivaire à votre domicile.

Si non, n'accepte pas le prélèvement (P1=non)

Votre participation à cette recherche est précieuse. Nous vous remercions d'avoir répondu au questionnaire.

A tous

Commentaires éventuels

.....

Annex 19: Calculation of frequency for alternating and irregular night shift work in the C3-Nuit Study nested in the CONSTANCES cohort.

Alternating night shift work :

For the night work with alternating schedules, the number of nights worked during the job period was declared by the subjects, along with the number of days worked in the mornings, evenings, or days off. Then, the frequency of the night shift was calculated as a proportion of total work shifts/schedule, which gave an average frequency of nights worked in that particular job period relative to all shifts and days off. Following this, an average frequency of all alternating night shift jobs was calculated, weighing on the duration of each job period. The details on the calculation of frequency for alternating night shift work can be found in annex xx.

Frequency =(Number of nights *7)/ (number of mornings +number of afternoons +number of nights + number of work days off)

Irregular night shift work :

For the irregular night shifts, considering the possibility of heterogeneity in the occurrence of irregular nights during a job period, participants declared the frequency as the range of nights per week, per month, or even per year, depending on how often they work at night, which gave an average nights per week for every job (detailed calculation in annex xx). Following this, an average frequency of all irregular night shift jobs was calculated, weighing on the duration of each job period.

For irregular night shifts with other frequencies declared continuously, there were 4 options given to the respondents

- i. one or more times a week
- ii. one or more times a month
- iii. less than once a month

For each categories following values were assigned

- i. one or more times a week -> 2.8 nights/week

Assumptions : 1 to 5 times/week = 4 to 20 times/month = 48 to 240 times/year -> on average $((48+240)/2)*52 = 2.8$ times/week

- ii. one or more times a month (<1 time/week & >1 time/month) -> 0.5 nights/week

Assumptions: 1 to 3 times/month = 12 to 36 times/year -> average $((13+36)/2)*52 -> 0.5$ times/week

- iii. less than once a month -> 0.1 night /week

Assumptions = 1 to 11 times/year -> average $((1+11)/2)*52 -> 0.1$ times/wk

Annex 20: Odds ratios and 95% CI for associations between breast cancer risk and variables considered in the C3-Nuit Study nested in the CONSTANCES cohort.

	Cases (n = 671)	Controls (n = 1016)	OR (95% CI)
Age at reference			
Mean ± SD	56.8 ± 10.2	56.7 ± 10.5	1.00 (0.99-1.01)
Occupation, n(%)			
Blue-collar jobs/ Farmers	14 (2.1)	31 (3.1)	Ref
Intermediary jobs	219 (32.6)	367 (36.1)	1.32 (0.69-2.54)
Managers/white-collar jobs	382 (56.9)	535 (52.7)	1.58 (0.83-3.01)
Never worked /others	24 (3.6)	37 (3.6)	1.44 (0.64-3.24)
Missing	32 (4.8)	46 (4.5)	
Education, n(%)			
Primary education or lower	56 (8.4)	97 (9.6)	Ref
Secondary education	188 (28.0)	312 (30.7)	1.05 (0.72-1.54)
Undergraduate degree	204 (30.4)	288 (28.4)	1.25 (0.85-1.84)
University degree	223 (33.2)	319 (31.4)	1.24 (0.85-1.81)
BMI (kg/m²), n(%)			
<18.5	15 (2.2)	35 (3.4)	Ref
18.5-4.9	374 (55.7)	586 (57.5)	1.50 (0.81-2.78)
25-29.9	187 (27.9)	262 (25.8)	1.67 (0.89-3.16)
≥30	84 (12.5)	119 (11.7)	1.66 (0.85-3.23)
Missing	11 (1.6)	17 (1.4)	
Physical activity, n(%)			
Sedentary or low physical activity	7 (1.0)	12 (1.2)	Ref
Moderately active	417 (62.2)	581 (57.2)	1.47 (0.55-3.95)
Active	226 (33.7)	379 (37.3)	1.21 (0.45-3.27)
Highly active	21 (3.1)	44 (4.3)	1.16 (0.38-3.54)
Tobacco smoking, n(%)			
Non-smokers	316 (47.1)	546 (53.7)	Ref
Current smokers	119 (17.7)	130 (12.7)	1.68 (1.26-2.24)
Former smokers	224 (33.4)	294 (28.8)	1.37 (1.10-1.71)
Missing	12 (1.8)	46 (4.5)	
Recent alcohol consumption, n(%)			
Never drinkers	19 (2.8)	44 (4.3)	Ref
Moderate drinkers	512 (76.3)	776 (76.4)	1.53 (0.88-2.65)
Heavy drinkers	99 (17.8)	116 (11.4)	1.98 (1.09-3.62)
Missing	41 (6.1)	80 (7.9)	
History of maternal breast cancer, n(%)			
No	556 (82.9)	920 (90.5)	Ref
Yes	110 (16.4)	74 (7.3)	2.50 (1.83-3.42)
Missing	5 (0.7)	25 (2.2)	
Age at menarche, n(%)			
<12 years	186 (27.7)	252 (24.8)	1.41 (1.09-1.83)
12-14 years	301 (44.9)	412 (40.5)	1.40 (1.11-1.76)
≥14 years	184 (27.4)	352 (34.7)	Ref

	Cases (n = 671)	Controls (n = 1016)	OR (95% CI)
Parity, n(%)			
Nulliparous	86 (12.8)	148 (14.5)	Ref
1-2 children	381 (56.8)	543 (53.4)	0.84 (0.62-1.13)
≥3 children	166 (24.7)	249 (24.5)	0.95 (0.75-1.20)
Missing	38 (5.7)	77 (7.6)	
Age at 1st First pregnancy ^a			
<30 years	394 (72.0)	583 (73.6)	Ref
≥30 years	153 (28.0)	209 (26.4)	1.09 (0.85-1.40)
Breastfeeding, n(%)^a			
Yes	363 (66.4)	536 (67.7)	Ref
No	168 (30.7)	233 (29.4)	0.92 (0.74-1.14)
Missing	16 (2.9)	23 (2.9)	
Use of oral contraceptive pills, n(%)			
No	97 (14.5)	149 (14.7)	Ref
Yes	515 (76.8)	762 (75.0)	0.96 (0.73-1.28)
Missing	59 (8.7)	105 (10.3)	
Menopausal status at inclusion, n(%)			
Pre-menopausal	268 (39.9)	380 (37.4)	Ref
Post-menopausal	403 (60.1)	636 (62.4)	0.73 (0.52-1.03)
Menopausal hormonal therapy use, n(%)^b			
Never used	156 (38.7)	243 (38.2)	Ref
Former user	80 (19.9)	147 (23.1)	1.64 (1.07-2.540)
Current user	55 (13.7)	51 (8.0)	1.42 (0.99-2.07)
Missing	112 (27.7)	195 (30.7)	
Chronotype			
Evening	205 (30.6)	306 (30.1)	Ref
Neutral	116 (17.3)	215 (21.2)	0.81 (0.60-1.07)
Morning	350 (52.1)	495 (48.7)	1.06 (0.84-1.32)

Annex 21: Night shift work by type of occupation in the C3-Nuit Study nested in the CONSTANCES cohort.

Occupation	Night shift work		Total
	Never	Ever	
Farmers and blue collar jobs	37 (2.5)	8 (8.7)	45
Auto entrepreneur and intermediary jobs	491 (33.4)	95 (43.8)	586
Managerial jobs and white collar jobs	822 (55.9)	95 (43.8)	917
Others	53 (3.6)	8 (8.7)	61
Missing	67 (4.6)	11 (5.1)	78

Contexte et objectifs

Le cancer du sein (CS) est une maladie complexe et hétérogène influencée par une multitude de facteurs, y compris des facteurs génétiques, hormonaux et liés au mode de vie ^{5,23}. Il s'agit du cancer le plus fréquemment diagnostiqué et de la première cause de décès par cancer chez les femmes dans le monde ²⁹. En 2020, 2,3 millions de nouveaux cas ont été recensés à l'échelle mondiale ³⁰. L'incidence est plus élevée dans les pays à revenu élevé, tandis que les taux de mortalité sont plus élevés dans les pays à faible revenu en raison des diagnostics tardifs et de l'insuffisance des ressources de traitement. En France, le CS reste le cancer le plus courant chez les femmes, avec 61 000 nouveaux cas et 12 000 décès en 2023. L'incidence a augmenté, en partie en raison des changements dans le mode de vie et les facteurs reproductifs, tandis que la mortalité a diminué grâce aux avancées dans le traitement et le dépistage précoce ³⁵.

Les facteurs de risque du CS sont multiples. L'âge avancé, les facteurs génétiques et les antécédents familiaux de CS sont d'importants facteurs de risque ²³. Certains facteurs hormonaux et reproductifs, tels que la ménarche précoce, la ménopause tardive et l'utilisation de thérapies hormonales de substitution (THS), sont associés à une augmentation du risque de CS. Les facteurs liés au mode de vie, tels que l'obésité, en particulier après la ménopause ²³, l'inactivité physique, la consommation d'alcool et le tabagisme, sont également associés à un risque accru de cancer du sein ^{67,76,85}. Par ailleurs, plus la première grossesse menée à terme a lieu tôt, plus le risque de CS est diminué ⁵⁶. L'allaitement prolongé a aussi un effet protecteur sur le risque de CS ⁶¹. Bien que les effets de l'alimentation soient difficiles à mesurer, une consommation élevée de fruits, de légumes et de céréales complètes, pourrait avoir un effet protecteur, tandis qu'un régime riche en graisses et en aliments transformés pourrait augmenter le risque de CS ^{23,67,91}.

Les facteurs environnementaux, tels que l'exposition à la pollution de l'air, au bruit et à la lumière nocturne ^{99-101,128}, sont des domaines de préoccupation émergents, des études suggérant une possible association avec un risque accru de CS. Par ailleurs, le travail de nuit a été classé comme probablement cancérigène ⁹⁷. Les rythmes circadiens sont des cycles naturels de 24 heures et ils sont régulés par l'horloge interne du corps, principalement

contrôlée par les noyaux suprachiasmatiques (NSC) de l'hypothalamus ¹¹⁹. Ces rythmes synchronisent les fonctions physiologiques, telles que les cycles veille-sommeil, la production de mélatonine et le métabolisme, sur le cycle lumière-obscurité externe ¹¹⁹. La mélatonine atteint un pic pendant la nuit pour favoriser le sommeil, contribuant ainsi à la régulation du rythme circadien. Elle possède aussi des propriétés inhibitrices du cancer ¹²⁵. Les perturbations circadiennes réduisent la sécrétion de mélatonine et retardent son pic nocturne, ce qui entraîne des troubles du sommeil et en diminue les effets protecteurs ¹²⁵. Les études épidémiologiques montrent une association significative entre les perturbations circadiennes et un risque accru de cancer, notamment de CS.

L'évaluation directe de la perturbation circadienne dans les études épidémiologiques étant complexe et coûteuse, le travail de nuit et l'exposition à la lumière nocturne peuvent servir d'indicateur.

Travail de nuit : Il se définit comme un emploi exercé pendant les heures de sommeil habituelles de la population générale, entre 23 heures et 7 heures ¹³⁸. Le travail de nuit peut être fixe / permanent, alternant / rotatif ou irrégulier, selon le type d'horaires. Chacun de ces types perturbe les rythmes circadiens naturels en modifiant l'alternance jour-nuit. Sur les deux dernières décennies, à l'échelle mondiale et en Europe, environ 20% des employés travaillent de nuit ¹⁴⁵. L'enquête de 2021 sur les conditions de travail en Europe a montré une augmentation du travail de nuit au cours de la dernière décennie (38 % des employés travaillant la nuit en Europe et 35 % en France) ¹⁴⁸. En 2007, le Centre International de Recherche sur le Cancer (CIRC) a classé le "travail posté impliquant une perturbation circadienne" comme "probablement cancérigène pour l'homme" (Groupe 2A), classification reconfirmée en 2020 ⁹⁷. Le rapport du CIRC suggérait que le mécanisme cancérigène potentiel lié au travail de nuit découle de la désynchronisation entre les phases lumière-obscurité externes et le rythme circadien endogène due à l'exposition à la lumière artificielle la nuit, aux modifications des niveaux d'activité, de l'état d'alerte, des fonctions cognitives et des horaires de repas modifiés par les horaires de travail de nuit 2020 ⁹⁷. Il a été suggéré de définir le travail de nuit comme "travailler au moins trois heures entre minuit et 5 heures du matin" comme un minimum d'exposition requis pour estimer la perturbation du sommeil créée par le travail de

nuit ¹³⁸. De plus, les différents aspects du travail de nuit (durée, intensité et horaires) peuvent expliquer son impact sur les perturbations chronologiques ¹³⁸.

La lumière la nuit : La lumière artificielle (LAN) provenant de lampadaires, panneaux publicitaires et appareils électroniques crée une "pollution lumineuse"¹⁷¹. Cette pollution se traduit par l'éclairement du ciel nocturne, les intrusions lumineuses, l'éblouissement et la sur-illumination et impacte les environnements intérieurs et extérieurs ¹⁷². Avec l'usage croissant de l'éclairage électrique, plus de 80 % de la population mondiale vit sous des ciels pollués par la lumière ¹⁸⁴, et la France a observé une forte augmentation de l'éclairage nocturne ces dernières décennies.

L'évaluation de la LAN est complexe, utilisant divers outils allant des satellites aux instruments au sol ^{174,178}. Les évaluations via les images satellites sont couramment utilisées en épidémiologie, malgré des limites comme la résolution et la saturation des données ^{174,178}. Les méthodes aéroportées et au sol sont des approches alternatives. Elles sont coûteuses et ont une couverture spatiale réduite. Dans le spectre de la lumière visible, la lumière bleue (~480 nm) est particulièrement perturbante pour les rythmes circadiens et la production de mélatonine ¹⁷⁶. L'exposition à la LAN serait associée à des troubles du sommeil, de l'humeur, au syndrome métabolique, et à un risque accru de maladies telles que le CS. L'exposition à la LAN est particulièrement préoccupante en milieu urbain, où elle se combine avec d'autres expositions environnementales (pollution de l'air et bruit).

Les résultats des études épidémiologiques utilisant des données satellites ont rapporté une association positive entre une exposition élevée à la LAN et un risque accru de CS ¹¹⁹. Par ailleurs, certaines études n'ont pas trouvé d'association après avoir pris en compte des facteurs environnementaux. Une méta-analyse de huit études sur la LAN et le risque de CS a trouvé une estimation du risque global de 1,11 (IC 95 % : 1,07-1,16) pour les personnes ayant l'exposition la plus élevée à la LAN par rapport à la plus basse ¹⁸⁰. Les études incluses sont cependant hétérogènes dans les méthodes d'évaluation de l'exposition, la durée d'exposition, la population étudiée et le contrôle des facteurs de confusion. Malgré les nombreuses études explorant la relation entre le travail de nuit, l'exposition à la LAN et le risque de CS, des conclusions définitives restent difficiles à établir en raison de limites et lacunes dans la

recherche. Ces limites incluent des incohérences dans les méthodes d'évaluation de l'exposition, un contrôle insuffisant des variables de confusion, et une variabilité des modèles d'études. Cette thèse visait à étudier le rôle de l'exposition environnementale à la LAN et celui du travail de nuit dans le risque de CS en tenant compte des facteurs de confusion potentiels à partir d'études françaises.

Les objectifs de cette thèse étaient :

1. Étudier le rôle de l'exposition environnementale à la LAN sur le risque de CS dans l'étude cas-témoins CECILE.
2. Étudier le rôle de l'exposition environnementale à la LAN sur le risque de CS dans la cohorte prospective E3N-Génération
3. Étudier le rôle du travail de nuit sur le risque de CS dans la cohorte CONSTANCES.

Méthodes et matériels

Pour le premier objectif, nous nous sommes appuyés sur les données de l'étude CECILE, une étude cas-témoins menée dans deux départements français où les femmes ont été recrutés entre 2005 et 2007. Les cas ont été sélectionnés dans les centres hospitaliers de l'Ille et Vilaine et de la Côte d'Or, tandis que les témoins ont été sélectionnés dans la population générale selon un appariement par fréquence (tranches d'âge de 10 ans). Sur les 1556 cas identifiés, 1232 (79,3 %) ont été inclus, tandis que 1315 des 1731 témoins éligibles (76 %) ont été inclus dans l'étude. Des entretiens en face à face basés sur des questionnaires standardisés ont permis de recueillir des informations détaillées sur les caractéristiques sociodémographiques, les antécédents médicaux et familiaux, les facteurs reproductifs et hormonaux, les comportements liés au mode de vie, ainsi que l'histoire résidentielle et professionnelle des participantes. Toutes les adresses résidentielles des 10 années précédant le diagnostic ont été géocodées (BD Adresse for ArcGis).

Pour évaluer l'exposition à la LAN extérieure, les images satellites du Defense Meteorological Satellite Program (DMSP) ont été utilisées et croisées avec les adresses géocodées des femmes. Cela a permis de calculer l'exposition à la LAN extérieure des adresses résidentielles

sur les 10 années précédant le diagnostic des cas ou la date de référence. Parmi les 2548 femmes, 55 avaient des adresses ou des valeurs de LAN manquantes et 26 avaient des valeurs de LAN extrêmes (considérées comme des erreurs), ce qui a laissé 2467 femmes (1185 cas et 1214 témoins) pour l'analyse principale.

Pour le deuxième objectif, nous avons utilisé les données d'une étude cas-témoins nichée dans la cohorte E3N-Génération. Cette génération comprends près de 100,000 femmes âgées de 40 à 65 ans lors de leur recrutement en France en 1990. Elles étaient adhérentes à la Mutuelle Générale de l'Éducation Nationale. Depuis 1990, des questionnaires auto-administrés sont envoyés aux participantes tous les 2-3 ans. Ils visent à recueillir des informations sociodémographiques, les antécédents médicaux et familiaux, les facteurs reproductifs et hormonaux, les comportements liés au mode de vie et l'histoire résidentielle des participantes. L'étude cas-témoins nichée comprenait tous les cas de CS incident survenus entre 1990 et 2011. Ces cas ont été appariés individuellement à des témoins en fonction de l'âge, de la date, du département de résidence et du statut ménopausique à l'inclusion. Toutes les adresses résidentielles ont été géocodées (Base BD Adresse for ArcGis). Les femmes ayant des données manquantes sur les variables d'appariement et leur paire ($n = 6$) ainsi que celles ayant des informations manquantes sur l'adresse ou résidant hors de la France continentale ($n = 2108$) ont été exclues, laissant 5222 cas de CS et 5222 témoins. L'exposition à la LAN extérieur a été évaluée à l'aide d'images satellites DMSP selon la même méthode que dans le premier objectif.

Pour le troisième objectif, nous avons utilisé les données de l'étude C3-Nuit, une étude cas-témoins nichée dans la cohorte CONSTANCES. Les participants sont des adultes français âgés de 18 à 69 ans au recrutement, sélectionnés de manière aléatoire. Ils ont été invités à un examen de santé et invités à compléter des questionnaires détaillés lors de leur inclusion et au cours du suivi. Des informations ont été recueillies sur les caractéristiques sociodémographiques, les antécédents personnels et médicaux et sur les expositions professionnelles et environnementales. L'étude C3-Nuit a été spécifiquement conçue pour étudier l'association entre le travail de nuit et le risque de cancer du sein, de la prostate et colorectal. Un questionnaire détaillé a été administré par téléphone, recueillant des informations sur l'historique professionnel, les horaires de travail de nuit, les habitudes de sommeil et les repas. Cette thèse traite uniquement les cas de CS. Ces derniers ont été

identifiés par auto-déclaration, par vérification via des données médicales et par consultation de la base du Système National des Données de Santé. Les témoins ont été appariés en fréquence et sélectionnés par échantillonnage de densité incidence. Sur 1200 cas de CS éligibles, 674 (56 %) ont été inclus, et 1024 des 1590 témoins identifiés (64 %) ont été inclus. Le travail de nuit a été défini comme le fait de travailler au moins 3 heures entre minuit et 5 heures du matin. Les participants ont été classés comme travailleurs de nuit fixes, alternants ou irréguliers en fonction de leurs horaires de travail. Plusieurs mesures d'exposition ont été évaluées, y compris la fréquence des quarts de nuit, la durée du travail de nuit, la longueur de chaque quart, et le nombre total de nuits travaillées au cours de la vie.

Des modèles de régression logistique ont été appliqués pour estimer les rapports de cotes (OR) et les intervalles de confiance (IC) à 95 % correspondants pour estimer l'association entre l'exposition à la LAN extérieure et le risque de CS en ajustant sur les facteurs sociodémographiques (âge, éducation, urbanisation...), reproductifs, hormonaux, ceux liés au mode de vie, et des facteurs environnementaux (pollution de l'air et indice de végétation par différence normalisée, NDVI).

Résultats

Dans l'étude CECILE, le modèle de base (ajusté sur l'âge, le département et l'urbanisation), a montré des OR modérément élevés dans le deuxième tertile (T2) 1,11 (IC à 95 % : 0,86-1,41) et le troisième tertile (T3) 1,25 (IC à 95 % : 0,95-1,63) d'exposition à la LAN extérieure par rapport au premier (T1). L'OR pour une augmentation d'un intervalle interquartile (IQR = 159,9 nW/cm²/sr) de l'exposition à la LAN était de 1,09 (IC à 95 % : 0,96-1,24). Après ajustement sur les facteurs reproductifs, ceux liés au mode de vie ainsi que sur le NO₂, les OR ont diminué à 1,05 ; (IC à 95 % : 0,81-1,37) pour le T2 et à 1,10 ; (IC à 95 % : 0,78-1,56) pour le T3. Des ajustements supplémentaires pour le PM_{2,5} ou le PM₁₀ ont également diminué les OR, bien que la réduction soit faible pour les PM₁₀.

Aucune preuve de modification d'effet en fonction du département, de l'urbanisation, de l'éducation, du statut ménopausique, du travail de nuit ou de l'IMC n'a été observée (p>0,05). L'association était plus forte pour le CS HER2+ (OR 1,56 ; IC à 95 % : 1,03-2,31).

Dans l'étude cas-témoins nichée dans la cohorte E3N-Génération, le modèle de base a montré une augmentation régulière des OR dans les 2^e, 3^e et 4^e quartiles d'exposition à la LAN extérieure par rapport au quartile le plus bas, avec un OR dans le 4^e quartile de 1,20 (IC à 95 % : 1,06-1,37). L'ajustement sur les facteurs reproductifs, hormonaux et liés au mode de vie ainsi que l'éducation a entraîné une réduction des OR. Aucune réduction supplémentaire des OR n'a été observée après ajustement pour le NO₂. L'ajustement sur le NDVI au lieu de la pollution de l'air a entraîné une réduction négligeable des estimations dans tous les quartiles. Nous avons également ajusté pour le NO₂ et le NDVI ensemble et n'avons observé aucun changement dans les estimations. Les OR pour l'augmentation d'un IQR de l'exposition à la LAN extérieure sont restés significativement élevés après ajustement pour le NO₂ (1,11, IC à 95 % : 1,04-1,18) ainsi qu'après ajustement pour le NO₂ et le NDVI (1,12, IC à 95 % : 1,03-1,21). Aucune preuve de modification d'effet selon le statut ménopausique, l'urbanisation, le NDVI ou la pollution de l'air n'a été trouvée. Les OR selon les sous-types de tumeurs ER+ et PR- étaient légèrement supérieurs par rapport aux autres sous-types.

Dans l'étude C3-Nuit, les modèles d'ajustement de base n'ont montré aucune association entre le travail de nuit et le risque de CS (tous types, OR : 1,08, IC à 95 % : 0,81-1,45). Un ajustement supplémentaire sur les facteurs reproductifs et hormonaux ainsi que sur les facteurs liés au mode de vie et l'éducation a entraîné un changement négligeable de l'OR : 1,06 (IC à 95 % : 0,78-1,43). Chez les femmes ayant travaillé en alternance de nuit par rapport à celles qui n'ont jamais travaillé de nuit, l'OR était plus élevé (1,36, IC à 95 % : 0,85-2,27) aussi bien pour les quarts fixes ou irréguliers que pour les sous-types combinés. Les OR associés à d'autres caractéristiques du travail de nuit, telles que la durée, la fréquence, la longueur des quarts, et le nombre total de nuits travaillées au cours de la vie, n'ont pas révélé d'association claire. Cependant, quel que soit le critère d'exposition utilisé, des OR ont été trouvés plus élevés pour le travail de nuit en alternance que pour les quarts fixes ou irréguliers, surtout lorsque les quarts en alternance ne dépassaient pas trois nuits consécutives (OR : 2,73, IC à 95 % : 1,24-5,99).

L'OR associé au travail de nuit était plus élevé chez les femmes ménopausées que chez les femmes préménopausées, ainsi que chez les femmes ayant un chronotype du matin par rapport à celles ayant un chronotype neutre ou du soir. Nous avons également trouvé une

association positive chez les femmes ayant commencé à travailler en alternance de nuit avant leur première grossesse (OR : 1,99, IC à 95 % : 1,10-3,59).

Discussion

Dans les études CECILE et E3N-génération, nous avons observé des OR légèrement plus élevés de cancer du sein associés à l'exposition à la LAN extérieure, même après ajustement sur d'autres co-expositions environnementales. Ces études suggèrent que le risque est plus élevé chez les femmes ménopausées que chez les femmes en pré-ménopause, avec une association plus marquée pour le sous-type HER2+ dans l'étude CECILE. L'étude C3-Nuit n'a pas montré d'association entre le travail de nuit et le CS, mais les estimations du risque étaient plus élevées chez les femmes travaillant en horaires de nuit alternant. Les associations étaient également plus élevées chez les femmes ménopausées, celles ayant un chronotype matinal, et celles ayant commencé à travailler de nuit avant leur première grossesse.

Dans l'ensemble, les résultats de cette thèse suggèrent que l'exposition à la LAN extérieure et au travail de nuit, particulièrement en travail alternant, pourraient contribuer au risque de cancer du sein, soutenant l'hypothèse d'un effet des perturbations circadiennes dans le risque de cancer du sein suggérée par Stevens en 2006 ²⁴⁴. Ce dernier met en avant que la perturbation circadienne induite par la LAN conduit à une suppression de la production de mélatonine, augmentant ainsi le risque de cancer hormono-dépendant comme le CS ²⁴⁴.

Comme dans nos deux études, les études de la littérature ont eu recours aux images satellites DMSP pour estimer l'exposition à la LAN et elles ont rapporté une augmentation légère mais significative du risque de CS chez les femmes les plus exposées par rapport à celles moins exposées ^{200,202-204,206}. Cependant, d'autres études n'ont montré aucune augmentation du risque ^{182,199,201,205}. Les images satellites DMPS considèrent uniquement la lumière visible, or, l'étude espagnole de Garcia-Saenz et al., a évalué l'exposition à la lumière bleue en utilisant des images de la Station Spatiale Internationale (ISS) ¹⁸². Cette étude utilise l'indice de suppression de la mélatonine (MSI) et a démontré un risque plus élevé de CS associé à la lumière bleue ¹⁸². Ce résultat renforce l'observation que la lumière bleue est la composante spectrale la plus efficace pour la production nocturne de mélatonine ²⁵⁰, ce qui pourrait potentiellement augmenter le risque de CS ²⁴⁵.

Les résultats des études sur la LAN extérieure varient en fonction de l'ajustement des covariables environnementales. Les recherches prenant en compte des facteurs comme la pollution de l'air, le bruit et la verdure ont souvent montré une absence d'association. Il est nécessaire de considérer ces expositions concomitantes, car elles sont certainement corrélées avec la LAN extérieure, rendant l'examen de la LAN seule complexe.

Dans l'étude C3-Nuit, bien que l'exposition au travail de nuit ait été évaluée selon une définition standardisée du CIRC ¹³⁸, aucune association globale avec le risque de CS n'a été trouvée, contrairement aux études cas-témoins antérieures qui avaient observé une telle association ^{154,156,159,161,163,168}. Cependant, notre étude suggère que les quarts alternants pourraient augmenter ce risque, en particulier chez les femmes ayant un chronotype du matin, qui semblent plus vulnérables aux perturbations circadiennes ¹³².

Une analyse groupée de cinq études cas-témoins utilisant également la définition standardisée du CIRC a indiqué un risque global accru de cancer du sein chez les travailleuses de nuit ¹⁶³. Notre étude, l'une des rares ^{154,169,267} à examiner le risque de cancer du sein selon les types d'horaires, suggère que les quarts alternants pourraient augmenter ce risque en perturbant fortement le rythme circadien.

Le travail de nuit implique divers comportements et facteurs environnementaux, tels que des modifications du sommeil, des niveaux d'activité et des horaires de repas, qui ensemble perturbent le rythme circadien. Cependant, cette exposition reste spécifique à certains groupes professionnels, limitant la portée des résultats. En revanche, l'exposition à la LAN est plus répandue et touche une population plus large, indépendamment du contexte professionnel, ce qui en fait une mesure pertinente pour évaluer la perturbation circadienne à l'échelle de la population.

Malgré un objectif commun, nos études présentent des différences méthodologiques importantes. Dans l'étude CECILE, un biais de sélection potentiel est à noter, les cas ayant été plus souvent recrutés dans des zones urbaines que rurales, ce qui a pu entraîner une surreprésentation des cas exposés à la LAN extérieure ²³². Ce biais a été atténué par un ajustement sur l'urbanisation dans les analyses.

Une des sources potentielles de biais d'information dans cette thèse est l'utilisation des images satellites du DMSP pour l'évaluation de la LAN extérieure. Ces images présentent plusieurs limites à savoir une faible résolution, une possible saturation de l'exposition dans les zones urbaines, et une non-différenciation entre les longueurs d'onde spectrales ¹⁸¹, ce qui pourrait probablement entraîner une classification erronée de l'exposition. Cependant, cette classification est non différentielle - affectant les cas et les témoins de manière égale. Pendant les périodes de nos études (CECILE : 2005-2007, E3N-Génération : 1990-2011), des images ISS à plus haute résolution n'étaient pas disponibles, le DMSP étant alors la seule source de données disponible. Néanmoins, l'utilisation d'images radiométriquement calibrées ²¹⁹ a permis de réduire la classification potentiellement erronée de l'exposition.

Dans l'étude C3-Nuit, l'exposition au travail de nuit a été évaluée rétrospectivement, soulevant la possibilité d'un biais de rappel ²⁷⁰. Néanmoins, les activités professionnelles auto-déclarées sont généralement considérées comme fiables et ne constituent pas une source de biais de rappel ²⁷². Une classification minutieuse de chaque période de travail a permis de réduire le risque de classification erronée de l'exposition.

Nous avons ajusté pour divers facteurs de confusion possibles, y compris des facteurs liés au mode de vie, reproductifs ou hormonaux, et des covariables environnementales, mais certains facteurs cruciaux, tels que l'exposition à la LAN intérieure, la pollution sonore, et d'autres perturbateurs circadiens comme les horaires de sommeil ou de repas, n'ont pas été pris en compte dans notre étude. Par conséquent, un biais potentiel dû à une confusion résiduelle reste possible. Bien que les trois études aient eu une taille d'échantillon suffisamment grande, certaines estimations étaient basées sur un petit nombre de cas et de témoins, et certaines analyses de sous-groupes avaient une faible puissance statistique, conduisant à des imprécisions et à de larges intervalles de confiance.

Pour conclure, les résultats de cette thèse suggèrent que l'exposition à la LAN extérieure et au travail de nuit, particulièrement en travail alternant, pourraient contribuer au risque de cancer du sein, soutenant l'hypothèse d'un effet des perturbations circadiennes dans le risque de cancer du sein. Cependant, les limites méthodologiques, les erreurs de classement sur l'exposition ou d'éventuels effets de confusion résiduelle ont pu affecter la validité des

associations observées. Ces résultats nécessitent confirmation par de futures études utilisant des méthodes avancées d'évaluation de l'exposition.

Titre : Exposition à la lumière artificielle extérieure la nuit, travail de nuit et risque de cancer du sein ; résultats de trois études : CECILE, E3N-Génération et CONSTANCES
Mots-clés : lumière artificielle nocturne, travail de nuit, cancer du sein, perturbation circadienne, épidémiologie, étude cas-témoin

Contexte : L'incidence du cancer du sein est en constante augmentation. La modernisation rapide des sociétés et le marché du travail ont entraîné une exposition accrue à la lumière artificielle nocturne (LAN) et au travail de nuit. Ces facteurs contribuent à la perturbation du rythme circadien, un facteur de risque potentiel pour les cancers hormono-dépendants comme le cancer du sein. La littérature sur le travail de nuit, la LAN extérieure et le risque de cancer du sein reste incohérente en raison des différences entre les méthodes d'évaluation de l'exposition et la prise en compte des facteurs de confusion. Cette thèse vise à étudier le rôle de l'exposition environnementale à la LAN et celui du travail de nuit sur le risque de cancer du sein en tenant compte des facteurs de confusion potentiels, à partir d'études en France.

Méthodes : L'association entre la LAN extérieure et le risque de cancer du sein a été étudiée dans l'étude cas-témoins en population, CECILE (1185 cas et 1218 témoins), et dans l'étude cas-témoins nichée dans la cohorte prospective E3N-Génération (5222 cas et 5222 témoins). L'exposition à la LAN extérieure a été évaluée à l'aide d'images satellite du programme américain de satellites météorologiques (Defense Meteorological Satellite Program). L'association entre le travail de nuit et le cancer du sein a été étudiée dans l'étude C3-Nuit, une étude cas-témoins nichée dans la cohorte CONSTANCES (671 cas et 1016 témoins). Une évaluation détaillée de l'exposition au travail de nuit a été réalisée à partir de l'historique professionnel. Des modèles de régression logistique ont été utilisés pour obtenir les estimations de risque, en tenant compte des principaux facteurs de confusion comme la pollution de l'air ou la proximité d'espaces verts (indice de végétation normalisé : Normalized Difference Vegetation Index).

Résultats : Dans l'étude CECILE et dans la cohorte E3N-génération, nous avons observé des odds ratios légèrement élevés de cancer du sein associés à l'exposition à la LAN extérieure qui persistaient après ajustement sur les co-expositions environnementales. Ces deux études suggèrent que le risque de cancer du sein lié à la LAN serait plus élevé chez les femmes ménopausées que chez celles en pré-ménopause. Une association plus marquée pour le sous-type de cancer du sein HER2+ a été observée dans l'étude CECILE. Dans l'étude C3-Nuit, aucune association entre le travail de nuit et le risque de cancer du sein n'a été observée globalement, mais les estimations de risque étaient plus élevées chez les femmes travaillant en horaires de nuit alternants. Les associations étaient plus prononcées chez les femmes ménopausées que chez les femmes pré-ménopausées, chez celles qui avaient un chronotype du matin par rapport à celles ayant un chronotype du soir ou neutre, et chez celles qui avaient commencé à travailler de nuit avant leur première grossesse.

Conclusion : Les résultats de cette thèse suggèrent que l'exposition à la LAN extérieure et au travail de nuit, particulièrement en travail alternant, pourraient contribuer au risque de cancer du sein, soutenant l'hypothèse d'un effet des perturbations du rythme circadien sur le risque de cancer du sein. Cependant, les limites méthodologiques, les erreurs de classement sur l'exposition, d'éventuels effets de confusion résiduels ont pu affecter la validité des associations observées. Ces résultats nécessitent confirmation par de futures études utilisant des méthodes avancées d'évaluation de l'exposition.

Title : Exposure to outdoor artificial light at night, working at night and the risk of breast cancer; Findings from three studies: CECILE, E3N-Generations and CONSTANCES
Keywords: artificial light at night, night shift work, breast cancer, circadian disruption, epidemiology, case-control study

Background: The incidence of breast cancer is increasing and is projected to continue rising. Rapid modernization and growth in the global workforce have increased exposure to artificial light at night (LAN) and night shift work. These factors contribute to circadian disruption, a potential risk factor for hormone-dependent cancers, including breast cancer. Directly assessing circadian disruption through biomarkers like melatonin in large-scale epidemiological studies is resource-intensive and time-consuming. Existing literature on night shift work, outdoor LAN, and breast cancer risk remains inconsistent due to variations in exposure assessment methods and inadequate adjustment for confounders. This thesis aims to investigate the role of environmental exposure to outdoor LAN and night shift work in breast cancer risk in the French population.

Methods: Three epidemiological studies were utilized to achieve the objectives. The association of outdoor LAN and breast cancer risk was studied using a population-based case-control study, CECILE (1185 cases and 1218 controls), and a nested case-control study within the prospective E3N-Generations cohort (5222 cases and 5222 controls). Outdoor LAN exposure was assessed using satellite images from the Defense Meteorological Satellite Program. The association between night shift work and breast cancer risk was studied using C3-Nuit, a nested case-control study within the CONSTANCES cohort (671 cases and 1016 controls). A detailed assessment of exposure to night shift work was conducted using a comprehensive questionnaire on occupational history.

Logistic regression models were used to obtain risk estimates adjusting for important confounders, including environmental exposure such as air pollution and residential greenness (Normalized Difference Vegetation Index)

Results: In the CECILE study and the E3N-Generations cohort, we found slightly increased odds ratios (ORs) of breast cancer associated with exposure to outdoor LAN that persisted after adjustment for environmental co-exposures. Both studies suggested a potential increased risk for post-menopausal women, while a stronger association for the HER2+ cancer subtype was found in the CECILE Study.

In the C3-nuit study, no clear association between night shift work and breast cancer risk was seen overall, but the ORs for breast cancer were increased among women working alternating night shifts. The associations were more pronounced among post-menopausal women than premenopausal women, those with morning chronotypes compared to evening or neutral chronotypes, and those who started night work before their first pregnancy.

Conclusions: The findings from this thesis suggest that both exposure to outdoor LAN and night shift work, particularly alternating night shift work, potentially contribute to breast cancer risk, supporting the hypothesis of the role of circadian disruption in breast cancer. However, methodological limitations, exposure misclassification, potential selection bias, and residual confounding may undermine the validity of the observed associations. These findings warrant confirmation through future studies with refined methodologies.