Impact of physical activity on return to work after cancer diagnosis : an evidence-based approach

Têtê Norbert Wilson

THESE DE DOCTORAT

DE
L'UNIVERSITÉ D'ANGERS
SOUS LE SCEAU DE
LA COMUE ANGERS – LE MANS

ECOLE DOCTORALE N° 605
Biologie-Santé
Spécialité : « *Santé Publique* »

Par
« Têtê Norbert WILSON »

« Impact of physical activity on return to work after cancer diagnosis: an evidence-based approach »

« Impact de l'activité physique sur le retour au travail après cancer : une approche basée sur les preuves »

Thèse présentée et soutenue à Angers, le 20 décembre 2023

Unité de recherche : Irset-Inserm UMR 1085-Equipe d'Epidémiologie en Santé au Travail et Ergonomie (Ester)

Rapporteurs avant soutenance :

Yolande ESQUIROL	Maître de Conférence d'Université - Praticienne Hospitalière, Université de Toulouse
Jean-François GEHANNO	Professeur d'Université - Praticien Hospitalier, Université de Rouen

Composition du Jury :

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Examinateurs :	**Koumavi EKOUEVI**	Professeur d'Université, Université de Lomé, Togo
	Yolande ESQUIROL	Maître de Conférences - Praticienne Hospitalière, Université de Toulouse
	Jean-François GEHANNO	Professeur d'Université - Praticien Hospitalier, Université de Rouen
	Mélanie BERTIN	Maitre de Conférences, Ecole des Hautes Etudes en Santé Publique (EHESP)
Dir. de thèse :	**Yves ROQUELAURE**	Professeur d'Université - Praticien Hospitalier, Université d'Angers
Co-dir. de thèse :	**Evanoff BRADLEY**	Professeur, Université de Washington à Saint Louis, Etats-Unis
	Agnès AUBLET-CUVELIER	Directrice des études, Institut National de Recherche et de Sécurité (INRS)
Invité :	**Bertrand PORRO**	Chercheur (PhD), Institut de Cancérologie de l'Ouest (ICO), Angers.

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ACKNOWLEDGEMENTS

First, I would like to express my greatest gratitude to my principal supervisor, **Prof. Yves Roquelaure**, for giving me an opportunity to carry out Ph.D. research under his supervision. You have taught me the basics of research and helped me through thick and thin to walk the path of Ph.D. Thank you for your support and scientific expertise which are particularly beneficial to me.

I would also like to thank my co-supervisors, **Dr. Agnès Aublet-Cuvelier, and Dr. Evanoff Bradley**, for their support, advice, and insightful comments on the different pieces of the research carried out during my thesis.

I would like to thank **Pr. Jean-François Gehanno** and **Dr. Yolande Esquirol** for accepting to be rapporteurs of this thesis. Thank you for the precious time you devoted to my dissertation, your valuable comments helped me to be perfect in research.

To **Pr. Audrey Petit, Pr. Koumavi Ekouevi,** and **Dr. Mélanie Bertin,** thank you for accepting to be examiners of this thesis.

I am very grateful to **Dr. Bertrand Porro** for your valuable support and insightful comments on the different pieces of the research. Your research experience helped me to get the right advice at the right time.

To **Dr. Aboubakari Nambiema**, you are present since the beginning of this thesis. Thank you for your advice, support, and coaching, which are very useful for me during the thesis.

I would especially like to express my gratitude and recognition to **Dr. Brad Hounkpati,** President of Grain de Sel Togo, Inc. for his support through a scholarship.

I also thank **Dr. Elom Aglago** and **Dr. Marc Fadel** for the proofreading of the English and valuable comments on the thesis dissertation.

My sincere thanks go to **Valérie Fierens**, for efficient administrative assistance during my thesis. Thank you for everything.

I thank all my colleagues of Ester team and everyone who participated in one way or another in the success of this doctoral thesis. I am very proud to be a member of the team.

To my friends **André Adandjesso**, **Gagnon Amouzouvi**, **Amen Akakpo-Vizah**, **Aristide Ayeko**, **Jean-Claude Amevor**, **Ayao Amedome,** and **Raphael Kinvi-Dossou**, for their valuable support during my thesis.

Lastly, I would like to express my profound gratitude to my parents, to my brothers, sisters, and all the family for their endless love, and continuous encouragement throughout my years of study and through my life in general. This accomplishment would not have been possible without them.

Summary

Research and activities during the thesis

1. Publications

1.1. Published article

Wilson, T.N., Nambiema, A., Porro, B., Descatha, A., Aublet-Cuvelier, A., Evanoff, B., Roquelaure, Y., 2023. *Effectiveness of Physical Activity Interventions on Return to Work After a Cancer Diagnosis: A Systematic Review and Meta-analysis.* J Occup Rehabil 33, 4–19. https://doi.org/10.1007/s10926-022-10052-9

Wilson, T.N., Roquelaure, Y., Evanoff, B. et al. *Physical activity in people diagnosed with cancer: a rapid review of recommendations and critical appraisal of international guidelines*. Support Care Cancer 31, 679 (2023). https://doi.org/10.1007/s00520-023-08123-5

1.2. Articles in progress

Wilson, T.N., Evanoff, B., Aublet-Cuvelier, A., Porro, B., Roquelaure, Y. *Practical protocols for prescribing and implementing adapted physical activity program to support return to work in breast cancer survivors.*

2. Scientific communications

2.1. Oral presentations

Wilson, T.N., Nambiema, A., Porro, B., Descatha, A., Aublet-Cuvelier, A., Evanoff, B., Roquelaure, Y. *Effect of physical activity interventions on return-to-work after cancer: what is the optimal dose needed?* International scientific conference "Cancer, Work and Employment". Paris, France, November 21-22, 2022.

Wilson, T.N., Nambiema, A., Porro, B., Descatha, A., Aublet-Cuvelier, A., Evanoff, B., Roquelaure, Y. *La dose d'activité physique nécessaire pour améliorer le retour au travail après cancer : méta-régression.* Journée Scientifique SFR-ICAT. Angers, France, June 08, 2022.

Wilson, T.N., Nambiema, A., Porro, B., Descatha, A., Aublet-Cuvelier, A., Evanoff, B., Roquelaure, Y. *La dose d'activité physique nécessaire pour améliorer le retour au travail après cancer : revue systématique et méta-régression.* 16ème conférence francophone d'Epidémiologie Clinique (EPICLIN) et les 29èmes Journées des Statisticiens des Centres de Lutte Contre le Cancer. Paris, France, May 18-20, 2022.

2.2. Poster presentations

Wilson, T.N., Roquelaure, Y., Evanoff, B., Aublet-Cuvelier, A., Porro, B. *Activité physique adaptée et retour au travail des patients diagnostiqués d'un cancer : Synthèse des recommandations et évaluation critique des directives internationales.* 17èmes journées du Cancéropôle Grand Ouest (JCGO-2023), Vannes, France, June 29-30, 2023.

Wilson, T.N., Nambiema, A., Porro, B., Descatha, A., Aublet-Cuvelier, A., Evanoff, B., Roquelaure, Y. *Effectiveness of physical activity interventions on return to work after a cancer diagnosis: a meta-analysis.* 25eme Journée Jeunes Chercheurs en Cancérologie. Paris, France, Novembre 18-19, 2021.

Wilson, T.N., Nambiema, A., Porro, B., Descatha, A., Aublet-Cuvelier, A., Evanoff, B., Roquelaure, Y. *Effectiveness of physical activity interventions on return to work after a cancer diagnosis: a systematic review and meta-analysis.* Journée scientifique des doctorants de l'Ecole doctorale Biologie Santé. Brest, France, December 09-10, 2021.

2.3. Scientific vulgarization (Fêtes des Sciences 2023)

Comic books and Escape Game: the results of my thesis were used to develop a comic strip and an Escape Game which are presented to a non-scientific public (i.e., children, teenagers, parents, visitors, etc.) during the science festival organized by University of Angers on October 14-15, 2023.

3. Responsibility during the thesis

Representative member of Ph.D. Students at the council of the SFR-ICAT, from November 2022 to October 2023.

Member of the board of Irset's Ph.D. and Post-doctoral Club (Doc'7), from October 2022 to September 2023.

Co-organizer of the 10th "***Printemps de la Recherche***" at Irset, April 14, 2023.

Member of the committee for organizing Ph.D. Student Scientific Days, December 10-11, in 2020.

Abbreviations, symbols, and central concepts

Abbreviations and symbols

APA	Adapted Physical Activity
AUD	Australian dollar
CI	Confidence interval
CRF	cancer related fatigue
€	Euro
EU	European Union
EU-27	The 27 countries of the European Union
FITT	Frequency, Intensity, Time, and Type of physical activity
GDP	Gross Domestic Product
HQoL	Health quality of life
IARC	International Agency for Research on Cancer
INT$	International Dollar
LMICs	Low- and Middle-Income Countries
MASCC	Multinational Association of Supportive Care in Cancer
PA	Physical Activity
QoL	Quality of life
RCT	Randomized clinical trial
RR	Relative risk
UADT	Upper aerodigestive tract
USA	United States of America
US$	United States Dollar
WHO	World Health Organization

Concept

RTW: "**Return To Work**". This abbreviation is used in work-related literature as a term for describing issues of returning to work after periods of sickness absence from work as a process and as an outcome (Young et al., 2005b). In the current thesis, the abbreviation is related to return to work after cancer and cancer treatment.

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CHAPTER 1: INTRODUCTION

1. Background and rational of the thesis

Cancer is one of the leading causes of burden, making it a major public health problem worldwide (WHO, 2022; Wild et al., 2020). Due to early detection of cancer and advances in treatment, the number of people diagnosed with cancer and those who survive is increasing (Shahid and Raza, 2023). In 2020, the number of cancer survivors was estimated at 50.6 million, and this number is expected to increase in the coming years (IARC, 2020). Among cancer survivors, around half are of working age and employed at the time of diagnosis (Ferlay et al., 2018; Miller et al., 2019).

However, cancer and its treatment have adverse effects on physical, psychological, and mental health of cancer patients (Grusdat et al., 2022; Stein et al., 2008). For instance, it was reported that many cancer survivors experience physical (e.g., fatigue, pain), emotional, and psychological (e.g., anxiety and depression) side effects caused by cancer and its treatments (Baden et al., 2020; Götze et al., 2020; Jefford et al., 2017). Some of these symptoms can persist for several months or years after the treatment, having negative impacts on the overall quality of life (QoL) and daily activities of cancer survivors (Schmidt et al., 2019; Taskila and Lindbohm, 2007). Addition, it has been shown that cancer and its treatment have significant negative impacts on the work ability (Horsboel et al., 2015) and the professional life of cancer survivors (Blinder and Gany, 2020; Thandrayen et al., 2022). Specifically, around 26-53% of employees diagnosed and treated for cancer are on sick leave, quit or lose their job, and have difficulties in returning to work (D. Kang et al., 2022; Mehnert, 2011; Park et al., 2008). An earlier review by de Boer et al. (de Boer et al., 2009) found that cancer survivors are 1.4 times more like to be unemployed compared to healthy people. Even 1 to 2 years after diagnosis, only 39 to 77% of cancer survivors are able to return to work (RTW) (Paltrinieri et al., 2018). These findings demonstrate that all cancer survivors do not RTW after cancer diagnosis and they often experience difficulties in the labor market (Rottenberg et al., 2016). Yet not returning to work or being unemployed has adverse consequences for cancer patients (e.g., loss of income)

(Hernandez and Schlander, 2021), their families, as well as society (e.g., disability pensions, and loss of productivity) (Meadows et al., 2010; Shakespeare, 2018). Considering all these problems experienced by cancer survivors, specifically the difficulties of returning to work after diagnosis, there is needed to support people diagnosed with cancer in their RTW process.

Several supportive care include physical activity (PA), nutritional support, counseling, music therapy, meditation are used for cancer patients. However, several reviews, meta-analyses, and studies have shown that PA is the most effective on the physical, mental, and psychological health of cancer survivors (Loprinzi and Cardinal, 2012; Myers et al., 2018; Piraux et al., 2020; Schwartz et al., 2017). Specifically, PA reduces cancer-related fatigue (CRF) (Belloni et al., 2021; X. Chen et al., 2023; Kessels et al., 2018), improves cardiorespiratory fitness and QoL of cancer survivors (Joaquim et al., 2022; Martínez-Vizcaíno et al., 2023). It has also been shown that PA improves patients' muscle strength, body composition (fat/lean mass), and body image (Padilha et al., 2017; Reis et al., 2023), as well as self-esteem (Landry et al., 2018). For women with early breast cancer, PA was associated with a better QoL, less depression and anxiety, and fewer adverse events of adjuvant therapy (Vehmanen et al., 2022). A recent study (an International Multidisciplinary Roundtable) including randomized controlled trials (RCTs), systematic reviews, and meta-analyses showed with strong evidence that aerobic and resistance training improve common cancer-related health outcomes, including anxiety, depressive symptoms, fatigue, physical functioning, and health-related quality of life (HRQoL) (Campbell et al., 2019). All these findings supported the evidence of the beneficial effects of PA on physiological function, physical and psychological health of cancer survivors. This evidence led several national and international organizations, scientific societies, and government agencies to develop guidelines that recommend PA as the best supportive care to address the cancer-related outcomes in survivors (Buffart et al., 2014; Campbell et al., 2012; Harris et al., 2012; Mustian et al., 2012; Segal et al., 2017).

In contrast, the evidence for the effectiveness of PA on RTW after a cancer diagnosis remains unclear (de Boer et al., 2015). Indeed, to date, only few studies in the literature have investigated the effect of PA on RTW in cancer survivors (Björneklett et al., 2013; Groeneveld et al., 2013; Hubbard et al., 2013; Lee et al., 2017; Leensen et al., 2017; Torregrosa et al., 2022; Van Waart et al.,

2015). The results from these primary studies are often contradictory and limited, as the studies involved small sample sizes (i.e., few participants) and are of limited quality (Algeo et al., 2021; Bilodeau et al., 2017; Hoving et al., 2009; Rosbjerg et al., 2021). As such, it is difficult to establish consistent evidence for the effectiveness of PA on RTW after cancer diagnosis. In addition, the best type of exercise and the dose of PA in terms of duration, frequency, and intensity appropriate to improve RTW remains unclear. Therefore, further studies are warranted to address these gaps. Furthermore, the methodological quality of guidelines that recommend PA for cancer survivors remains unknown, and it is unclear whether the recommendations from existing guidelines are applicable to improving RTW in cancer survivors.

2. Objectives of the thesis

To address the gaps identified through the literature, the main objective of this thesis was objective to evaluate the effects of PA programs or interventions on RTW in cancer survivors and provide evidence for the effectiveness of PA on RTW after a cancer diagnosis. To achieve the main objective, we defined the following three specific objectives:

Objectif 1: to assess the effectiveness of PA interventions on RTW in cancer survivors, compared to usual care, and to determine the dose of PA needed to improve this outcome.

Objectif 2: the second objective was to identify existing guidelines that recommend PA in people diagnosed with cancer and assess their quality,

Objectif 3: lastly, based on the results of the two studies, we aimed to propose a guidance with practical protocols for prescribing and implementing adapted physical activity (APA) program to support RTW in breast cancer survivors.

Three studies in the form of research article were conducted to address these objectives (**see chapter 4**).

3. Organization of the thesis

This thesis is organized into five chapters:

Chapter 1 deals with the background and rationale for conducting this thesis project and outlines its objectives.

Chapter 2 "state of the art" provides a general understanding of the three main concepts of the thesis (i.e., cancer, PA, and RTW after cancer diagnosis). This chapter starts with an overview of the epidemiological indicators of cancer, treatment modalities of cancers, the side effects of cancer treatment, the economic burden, and impacts of cancer on the work-life of cancer survivors. The next part of the chapter deals with the definitions and determinants of RTW (factors associated with RTW), as well as the importance of work for cancer survivors are explored. Then, the conceptual models of RTW are described. Lastly, the chapter ends with a brief description of PA.

Chapter 3 outlines the methodology used to achieve objectives of the thesis.

Chapter 4 represents the results section. These results are presented in the form of three research articles (published and in progress).

Finally, **chapter 5** presents the general discussion. First, the key findings are summarized, and the strengths and limitations of the thesis are outlined. Then, the chapter ends with the contributions of this thesis, perspectives as well as some recommendations for further research. The thesis ends with the conclusion that can be drawn from the research. **Figure 1** presents an overview of the thesis structure.

In this thesis, we refer to **Cancer survivors as** *"people who have been diagnosed with cancer, from the time of diagnosis to the end of life"* (Aziz, 2002). This includes people who has been diagnosed with cancer and continue to live after their diagnosis: persons who have been diagnosed recently, those who are waiting for treatment, those who are undergoing or completing active therapy and are currently still alive (i.e., patients in remission; patients living with recurrent, progressive, or metastatic cancer; and long-term survivors who have been cured of cancer) (Doose et al., 2022; Park et al., 2018; Surbone and Tralongo, 2016). In this thesis, frequently used synonyms for cancer survivors are ***"cancer patients, people diagnosed with cancer"***.

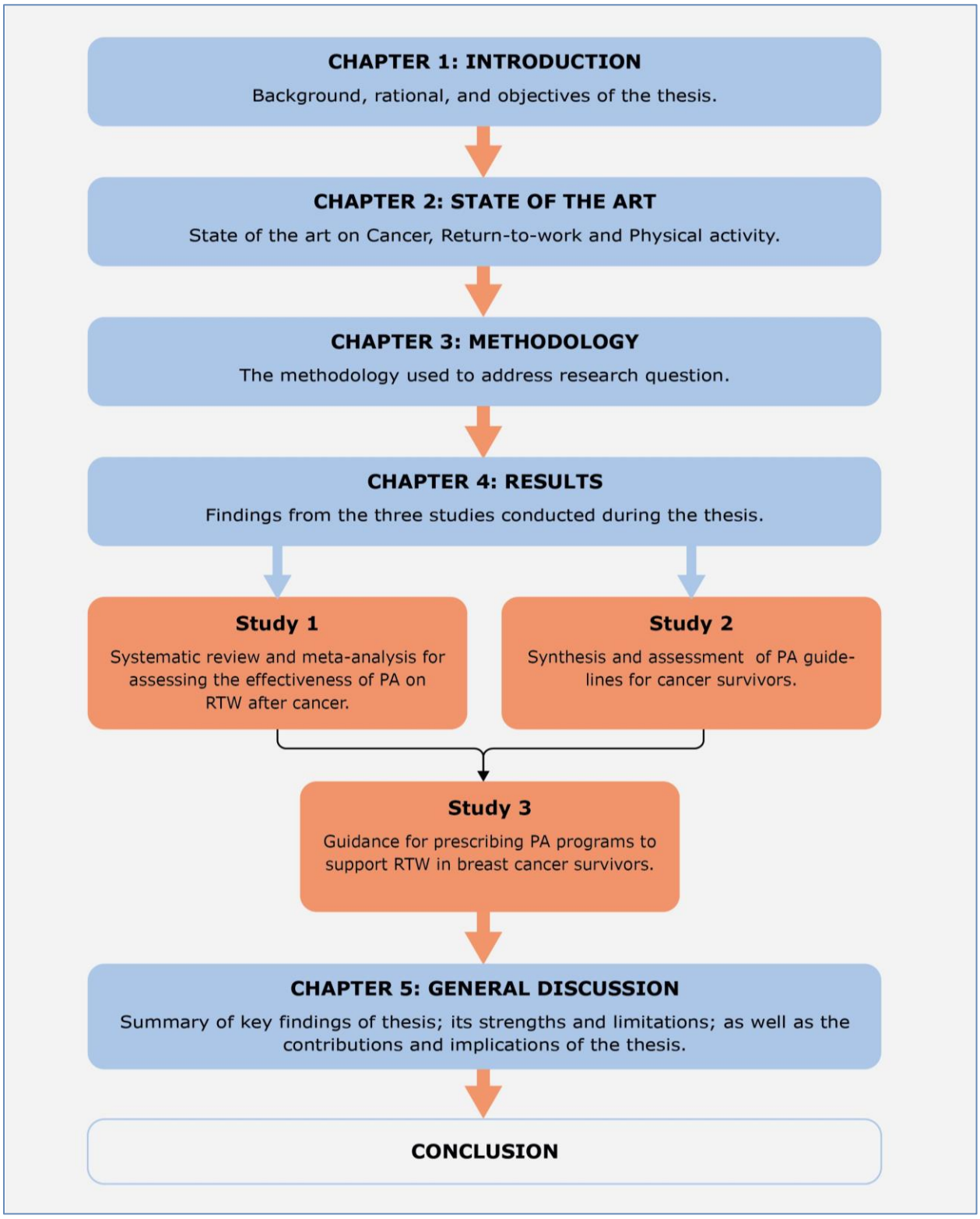

Figure 1. Overview of the structure of the thesis with the different chapters

CHAPTER 2: STATE OF THE ART

In this thesis, some key concepts such as **cancer, PA,** and **RTW** are used and require better understanding. As such the state of the art is conducted in order to clarify these main concepts.

1. Cancer

1.1. Definition and risk factors of cancer

Cancer is a group of diseases characterized by uncontrolled growth and proliferation of abnormal cells, due to genetic mutations following DNA damage (Cooper, 2000; WHO, 2022). This uncontrolled cell proliferation forms clusters of cells called tumors, which can arise from any tissue or organ in the body, multiply, and can go beyond their usual boundaries to invade surrounding tissues and/or spread to other organs (National Institutes of Health, 2007; WHO, 2022). There are many types of cancer according to the type of cell or tissue from which the tumor arises (histological type) (e.g., carcinomas, sarcomas, melanomas, lymphomas, leukemias, etc.) and the organ of origin (e.g., breast, lung, colorectal, stomach, liver, bladder, cervical cancers, etc.) (Cooper, 2000; National Cancer Institute, 2021a). Other common terms that can describe cancer are neoplasm and malignant tumors. **Table 1** shows the different types of cancers according to the tissue and organ from which they originate.

The exact etiology of cancer is unknown, but many factors are involved in the genetic mutation and contribute to the development of cancer. Several epidemiological and experimental studies have reported that external factors (lifestyle, environmental or occupational factors, infectious organism) (Lewandowska et al., 2019; Parsa, 2012), and internal factors (genetic factors, hormones, immune system dysfunction, etc.) (Wu et al., 2018), as well as individual factors (age, gender), may cause the development of cancer (National Cancer Institute, 2015; Pitot et al., 1981). These factors may interact together or sequentially to initiate carcinogenesis in the human body (Baba and Câtoi, 2007; Mathur et al., 2015).

Table 1. Different types of tumors with the tissue of origin and locations.

Type of tumors	Tissue or cell of origin	Location
Epithelial		
Adenocarcinoma	Derived from glandular epithelia	Breast, liver, kidney, prostate, ovary, thyroid, colon, stomach, salivary glands, lung.
Squamous cell Carcinoma	From transitional epithelia	
Carcinoma	From nonglandular epithelia	
Mesenchymal		
Sarcoma	Arises from cells of mesenchymal (connective tissue) origin (bone, muscle, cartilage, fat, vascular, …)	Bone, vessels, lymph nodes
Hematopoietic and lymphoreticular		
Lymphoma	Originates from B and T lymphocytes (tumors characterized by the presence of large, atypical cells)	Spleen, thymus, tonsils.
Leukemia	Bone marrow cells (blasts)	Blood cancer
Myeloma	Plasma cells of bone marrow (plasmocytes)	Bone marrow

Source : National Cancer Institute (National Cancer Institute, 2021a).

1.2. Epidemiology of cancer

According to the International Agency for Research on Cancer (IARC) report, the number of new cancer cases in 2020 is estimated at 19.3 million, and almost 10 million deaths related to cancer around the world (Sung et al., 2021). Out of these total cases, the most common diagnosed cancers worldwide were female breast (2.26 million cases, 11.7%), followed by lung (2.21 million, 11.4%), colorectal (1.88 million, 10.0%), prostate (1.41 million, 7.3%) and stomach cancers (1.08 million, 5.6%) (Sung et al., 2021). However, these estimates vary widely according to gender, age, and type of cancer. In sex-disaggregated data, the incidence ratio between men and women is greater than 1 for all cancers except thyroid cancer (i.e., 0.30) (Chhikara and Parang, 2022; Mattiuzzi and Lippi, 2019), reflecting the higher incidence in men. In men, the most common cancers diagnosed are lung (14.3%), prostate (14.1%), and stomach (7.1%) cancers, while in females the most frequently diagnosed cancers are breast (24.5%), lung (8.4%), and cervix (6.5%) cancers (Sung et al., 2021). About the mortality,

studies indicate that the leading causes of cancer deaths worldwide are malignancies of the lung (1.79 million deaths, 18.0% of total deaths), colorectal (935,173; 9.4%), liver (830,000; 8.3%), stomach (769,000; 7.7%), and breast cancer (680,000; 6.9%) (Ferlay et al., 2021; Sung et al., 2021). **Table 2** presents incidence and mortality of the most common (top 10) types of cancer cases in 2020 by sex illustrating the larger diversity between men and women.

Furthermore, there are also differences between regions and countries in incidence and mortality of cancers, reflecting geographical disparities. Indeed, incidence rates remain highest in the most developed regions, while mortality is relatively higher in developing countries, due to a lack of early cancer detection and access to treatment (Fidler and Bray, 2018; Vlad, 2023). For example, in 2020, the incidence of cancer in European countries (40 countries including the European Union, EU-27) is estimated at 4 million (around 21% of the total cancer cases) (Dyba et al., 2021; European Cancer Information System, 2020), compared with 1.1 million new cases in Africa (5.7% of global cancer incidence) (Sharma et al., 2022). In the United States (US), it was estimated to be approximately 1.8 million in 2020 (Siegel et al., 2020). For both sexes combined, it is estimated that more than half of all deaths occur in low- and middle-income countries (i.e., 58.3% of cancer deaths in Asia and 5.7% in Africa) in 2020, while Europe and the America will account for 19.6% and 14.2% of cancer deaths respectively (Sung et al., 2021).

With regard to cancer survival, the most recent estimates available in the literature are from the CONCORD-3[1] and SURVMARK-2 studies (Allemani et al., 2018; Arnold et al., 2019). According to the results of these studies, five-year cancer survival rates are increasing globally, but there are wide disparities across countries and between types of cancer. In most countries, the cancers with the lowest five-year survival estimates were pancreatic (5-15%), liver (5-30%), lung (10-20%), and brain cancer (20-40%) (Allemani et al., 2018). The highest five-year survival estimates were seen in patients with prostate cancer (70-100%), melanoma of skin

[1] **CONCORD** is the program for worldwide surveillance of trends in cancer survival, led by the London School of Hygiene & Tropical Medicine. It includes data for over 37·5 million patients diagnosed with cancer during the 15-year period 2000–14. Data were provided by more than 320 population-based cancer registries in 71 countries and territories. CONCORD-3 study includes 18 cancers or groups of cancers (Allemani et al., 2018).

(60-90%) and breast cancer (70% or above). It was also revealed that five-year net survival was generally higher in high-income countries such as the US, Canada, Australia, New Zealand, Finland, Iceland, Norway, and Sweden (Arnold et al., 2019). By contrast, survival is lower than elsewhere in Southeast Asia countries: India, Taiwan, China, Korea (Allemani et al., 2018). The steady increase in survival rates results in increased life expectancy for patients (i.e., more than 50% of patients survive five years after cancer diagnosis), making cancer a chronic disease (Batalik et al., 2021), with impacts on survivors' QoL.

Table 2. Estimated number of new cases (incidence) and deaths (mortality) for ten most common cancer types by sex worldwide in 2020*

	Number of new cases (% of all sites)			Number of new deaths (% of all sites)		
Cancer site	**Male**	**Female**	**Overall**	**Male**	**Female**	**Overall**
Breast	NA	2,261,419	2,261,419 (11.7)	NA	684,996	684,996 (6.9)
Lung	1,435,943	770,828	2,206,771 (11.4)	1,188,679	607,465	1,796,144 (18.0)
Colorectal**	1,065,960	865,630	1,931,590 (10.0)	515,637	419,536	915,880 (9.4)
Prostate	1,414,259	NA	1,414,259 (7.3)	375,304	NA	375,304 (3.8)
Stomach	719,523	369,580	1,089,103 (5.6)	502,788	266,005	768,793 (7.7)
Liver	632,320	273,357	905,677 (4.7)	577,522	252,658	830,180 (8.3)
Cervix uteri	NA	604,127	604,127 (3.1)	NA	341,831	341,831 (3.4)
Esophagus	418,350	185,750	604,100 (3.1)	374,313	169,763	544,076 (5.5)
Thyroid	137,287	448,915	586,202 (3.0)	15,906	27,740	43,646 (0.4)
Bladder	440,864	132,414	573,278 (3.0)	158,785	53 751	212,536 (2.1)

*Excludes non-melanoma skin cancer. Estimates by sex may not sum to the overall total due to rounding.
Calculated by adding cases of colon cancer and cases of rectal cancer. **NA: No applicable.

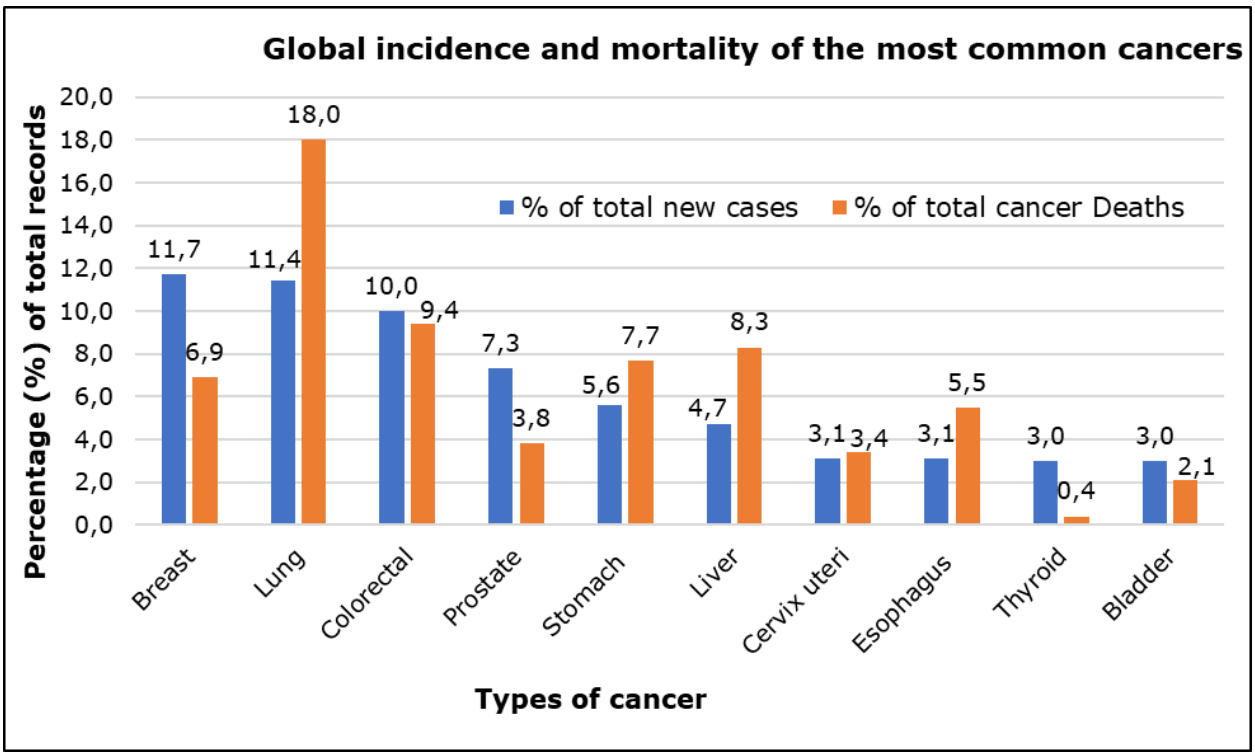

Figure 2. Relative representation of total new cases and total deaths for the ten most common cancer.

Data source: data used in the table 2 and figure 1 were retrieved from the Global Cancer Observatory (GLOBOCAN 2020 database).

1.3. Treatment of cancer

Once cancer is diagnosed, patients may often receive medical treatment for many months or years. The treatment aims to remove or destroy tumors in order to limit their growth and spread (Debela et al., 2021). It is often administered with the intent of curing the cancer or relieving the symptoms associated with the cancer, prolonging survival of patients, or preventing cancer recurrence (Miller et al., 2022). Several types of treatment are currently available for the management of cancer. These include local therapies such as surgery and radiation; and systemic therapies consist of chemotherapy, hormone therapy, immunotherapy, and targeted therapy (Debela et al., 2021). Often, treatments can be administered alone or in combination, based on patient and tumor characteristics (e.g., type of cancer, location, stage, severity, age, gender, co-morbidities, etc.), with the aim of achieving a more appropriate treatment for the patient (Abbas and Rehman, 2018).

Localized therapies refer to treatments used to treat specific parts of the body or tumor. Local therapy usually involves surgery and radiation therapy.

Surgery is the main traditional treatment indicated in the management of many solid tumors. The treatment of cancers by surgery consists in removing the tumor or reducing the size of the tumor as much as possible. Approximately 80% of patients diagnosed with cancer will be treated by surgery (Gillespie, 2011; MD Anderson Cancer Center, 2021). It may also be used in combination with other treatments such as chemotherapy or radiation therapy as part of an overall therapy plan.

Radiotherapy also called radiation therapy is a local treatment that uses high-powered energy beams, such as X-rays or protons, to kill cancer cells (Sharma et al., 2010; Shirzadfar and Khanahmadi, 2018). Its main goal is to deprive cancer cells of their multiplication potential (cell division). There are three ways to deliver radiation to the location of cancer (Jaffray and Gospodarowicz, 2015):

External beam radiation therapy: delivers high-energy rays directly to the cancer cells through beams of radiation outside the body,

Internal radiation or brachytherapy: is the implementation of solid radioactive nuclide (a species of an atom) in the patient's body directly within the tumor or near the cancerous tissue,

Radioisotope therapy: radiation is delivered through the systemic injection (orally or intravenously) of a radioisotope that has been designed to target a tumor.

Radiation therapy is one of the most common treatments for cancer, either alone or along with other forms of treatment. Approximately 50% of all cancer patients receive radiation therapy during their course of illness and it contributes to 40% of the curative treatment of cancer (Barton et al., 2014; Baskar et al., 2012).

Systemic therapies, while local treatment is directed at a specific area of cancer, systemic therapies are drugs that are administered through the bloodstream and potentially affect all parts of the body in order to destroy cancer cells anywhere they exist in the body (Miller et al., 2022). Systemic cancer therapy includes chemotherapy, hormone therapy, immunotherapy, and targeted therapy which are described below.

Chemotherapy involves the use of medicine or anti-cancer drugs (cytotoxic) to treat cancer. It is considered as the most effective and widely used treatment for many types of cancer (Abbas and Rehman, 2018). It can be used alone or in combination with other treatments (Boshuizen and Peeper, 2020; Debela et al., 2021). According to the study by Jacob and colleagues, the optimal chemotherapy utilization rates for individual tumor sites ranged from a low of 13% in thyroid cancers to a high of 94% in myeloma (Jacob et al., 2015). It can be administered before surgery with the goal to shrink tumors (neoadjuvant chemotherapy), and/or following surgery to eliminate any remaining cancer cells (adjuvant chemotherapy) (American Cancer Society, 2021).

Hormone therapy also called endocrine therapy is a treatment that uses medicines to block or decrease the level of the body's natural hormones that sometimes act to promote cancer growth (American Cancer Society, 2022). Hormone therapy aims to reduce the production of hormone and slow or stop the growth of a cancerous tumor (INCa, 2021). It is the most modern treatment usually used to treat hormone-dependent cancers such as breast, prostate, ovarian cancers, and womb cancer (also called uterine or endometrial cancer).

Immunotherapy known as biological therapy, uses substances made by the body or in a lab to stimulate a patient's immune system and help the body find and destroy cancer cells (Wahid et al., 2018). It includes monoclonal antibodies, interferons, biological response modifiers, tumor vaccines, and cell therapies. In the last few decades, immunotherapy has become an important part of treating some types of cancer (e.g., melanoma, kidney cancer, Merkel cell carcinoma, breast cancer, urothelial carcinoma, etc.) and has changed the life expectancy of a consistent number of patients (Botticelli et al., 2021). One of the most important aspects of immunotherapy is its lower toxicity compared to other drugs.

Targeted therapy is a new form of cancer treatment developed in recent years as a result of a deep knowledge of the molecular mechanisms leading to cancer. It is the cornerstone of precision medicine, which aims to offer patients a treatment tailored to the abnormalities of their tumor. In targeted therapy, drugs are used to block the growth and spread of cancer cells by interfering with specific molecules or proteins that are involved in the growth, and

spread of cancer (Kifle et al., 2021; Mathur et al., 2015). In contrast to other therapies, these drugs are administered to directly target cancer cells. Using targeted therapy markedly increased the survival rate for some cancer, for example going from a 17% survival rate to 24% in patients with advanced pancreatic cancer (Debela et al., 2021).

Supportive therapies or **supportive care** are treatments that do not directly treat cancer but are used to reduce side effects and address patient and family QoL concerns (American Cancer Society, 2022). They are defined by the Multinational Association of Supportive Care in Cancer (MASCC) as *"the prevention and management of the adverse effects of cancer and its treatment. This includes the management of physical and psychological symptoms and side effects across the continuum of the cancer experience from diagnosis through treatment to post-treatment care. Enhancing rehabilitation, secondary cancer prevention, survivorship, and end-of-life care are integral to supportive care*" (MASCC, 2022). Examples of supportive care include PA or exercise, nutritional support, counseling, music therapy, meditation, and palliative care.

1.3.1. The impacts of cancer and its treatment

a) The long-term and late adverse effects of cancer treatment

Treatments are not without adverse effects for patients. Thus, it has been reported that treatment cause often short or long-term side effects in cancer survivors (Gegechkori et al., 2017; Hack et al., 2015; Stein et al., 2008). Thus, most cancer survivors may experience physical, psychological, and cognitive symptoms due to treatment (**see Table 3**). These adverse effects occur according to the type of cancer; tumor stage; treatment modalities and the dose use; and from one person to another (Ahles and Root, 2018; Gegechkori et al., 2017; Stein et al., 2008). They may last for months or even years after and are the main predictors for not returning to work (Noeres et al., 2013). **Table 3** presents the synthesis of the main side effects associated with localized and systemic therapies of cancer.

Indeed, breast cancer, followed by colorectal cancer, lung cancer, and prostate cancer are among the largest groups of cancer associated with adverse and late effects (Bennett et al., 2018; Gegechkori et al., 2017; Noeres et al., 2013). Chemotherapy, surgery/anesthesia, and

radiotherapy are associated with fatigue and cognitive impairment that predicted lower future work ability[2] (Boelhouwer et al., 2023; Gegechkori et al., 2017; Országhová et al., 2021). Cognitive dysfunction can negatively affect mental functioning, including memory loss, aphasia, reduced reaction time, and concentration problems, lasting up to 20 years after cancer treatment (Brusletto, 2023; Fardell et al., 2023; Gegechkori et al., 2017; Koppelmans et al., 2012; Országhová et al., 2021). It has also been shown that chemotherapy, radiotherapy, and combination therapies are associated with psychosocial symptoms such as coping issues, anxiety, and depression, which influence the ability to work and have caused severe difficulties for people returning to work after cancer (Boelhouwer et al., 2021b; Lv et al., 2023; Mungase et al., 2021). The physical side effects of treatment, for example pain, neuropathy, reduced immune function, lymphedema, gastrointestinal problems, anemia and more, can also severely affect the ability to work (Gegechkori et al., 2017; Horsboel et al., 2015; Zomkowski et al., 2018). As a consequence, a decrease in QoL can result from reduced physical or emotional functioning and lead to an inability to retain work (Annunziata et al., 2018; Brusletto, 2023). Even with new therapies such as immune and hormone therapies, some side effects have been reported (Gegechkori et al., 2017). For instance, hormone therapy has disclosed a higher risk of infertility, osteoporosis, and fractures (Wentzensen and Trabert, 2015).

In this part, we highlighted that cancer and its treatment have numerous adverse effects that may impact the work-life of cancer survivors (reducing their work ability) (Boelhouwer et al., 2021b; Firkins et al., 2020). Therefore, it is necessary, after cancer diagnosis, to identify these symptoms and provide appropriate supportive care to alleviate them.

[2] **Work ability** refers to one's ability to be able to achieve expected work goals (Boelhouwer et al., 2021a; Ilmarinen, 2007).

Table 3. Summary of the most common long-term and late side effect of cancer treatment.

Treatment	Long-term and late effects
Chemotherapy	• Fatigue • Early menopause • Reduced of cardiorespiratory fitness • Increased risk of other cancers • Sexual side effects: infertility • Emotional difficulties: anxiety, depression • Peripheral neuropathy • Cognitive impairment: learning, memory, and attention difficulties; concentration problems • Osteoporosis
Radiation therapy	• Fatigue • Pain • Reduced of cardiorespiratory fitness • Emotional difficulties: anxiety, depression • Early menopause • Hypothyroidism • Increased risk of other cancers • Infertility • Lymphedema • Cognitive impairment • Osteoporosis
Surgery	• Fatigue • Lymphedema • Pain • Infertility • Menopause
Hormone therapy	• Fatigue • Blood clots • Menopausal symptoms • Osteoporosis • Sexual side effects: infertility, erectile dysfunction
Immunotherapy	• Fatigue • Muscle or joint pain • Osteoporosis
Targeted therapy	• Fatigue • Blood clots • Heart and vascular problems

Source: This table is adapted from American Cancer Society (American Cancer Society, 2019) and National Cancer Institute (National Cancer Institute, 2021b).

b) The impacts of cancer on work life

Apart from the side effects, cancer also negatively affect the work and work-life of cancer survivors (Blinder and Gany, 2020). In the following, we expose the impacts of cancer and its treatment on the professional life of cancer survivors.

Approximately 50% of people diagnosed with cancer are of working age or employed at the time of diagnosis (Ferlay et al., 2018; Miller et al., 2019). Following the cancer diagnosis and treatment, most patients are more likely to experience adverse work outcomes (Blinder and Gany, 2020; Duijts et al., 2014; Stone et al., 2017). Adverse work outcomes include all negative consequences of cancer on work, from smaller less impacting changes as reduced working hours, prolonged sick leave, delayed RTW, reduced work ability, and QoL at work, to major long lasting changes, such as disability pension, job loss, and unemployment, and everything in between (de Boer et al., 2023; Mehnert, 2011). It has been shown that cancer has negative impact on survivors' ability to work and job performance (e.g., cancer changed physical and cognitive functional ability) and lead them experiencing work-related distress (Stone et al., 2017). A systematic review including 64 studies found that between 26% and 53% of cancer survivors lost their job, quit working or have difficulties in returning to work over a 72-month period post diagnosis (Mehnert, 2011). A high proportion of patients experienced at least temporary changes in work schedules, work hours, wages, and a decline in work ability compared with people without cancer (Mehnert, 2011). A Study by Blinder and Gany (Blinder and Gany, 2020) also showed that most employees diagnosed with cancer reduced their working hours, extended sick leave, quit, or lost their jobs after diagnosis. Similarly, in the study by Banegas et colleagues, 54% of working-age cancer survivors reported that they are working full-time after being diagnosed (Banegas et al., 2016). Moreover, a study conducted in the USA showed that more than 40% of people (i.e., more than 3.5 million adults in the USA) who were employed at the time of diagnosis took extended leave or changed jobs after cancer diagnosis (de Moor et al., 2021). Among survivors who took extended leave, 75.4% took extended paid leave from work, most often during treatment (de Moor et al., 2021). Among survivors who changed jobs, 46.1% changed their schedule, role or career trajectory (de Moor et al., 2021). Changes included switching from a fixed to a flexible schedule (24.8%), moving from full- to part-time work or to a less demanding job (22.2%), not pursuing a promotion (16.7%),or retiring earlier than planned (15.3%) (de Moor et al., 2021).

It has also been shown that cancer survivors are less likely to work (Jeon 2017), have a significantly higher risk of unemployment, early retirement and are less likely to be re-employed compared with individuals never diagnosed with cancer (Mehnert, 2011; Rottenberg et al., 2016). In a recent systematic review and meta-analysis, the prevalence of unemployment after breast cancer surgery ranged from 5.6% to 56.3% (Wang et al., 2018). A Korean cohort study showed that working-age cancer survivors were 1.42 times more likely to be unemployed and had a 1.15 times lower rate of RTW than the general population (Choi and Lee, 2022). Similarly, a previous study conducted in Australia, including 34,393 patients diagnosed with cancer aged 25-64 years, showed that people with no health condition were 3 times more likely to be employed full-time compared to those diagnosed with cancer (Bates et al., 2018). In France, a study (using an administrative dataset) comparing women diagnosed with breast cancer with otherwise demographically similar healthy women, found that one year after diagnosis the probability of being employed decreased by 10% in women diagnosed with cancer, and down, to 12% five years later (Barnay et al., 2019). The above results are in accordance with a prior meta-analysis of 36 studies by de Boer et colleagues, which found that cancer survivors were 1.4 times more likely to be unemployed than healthy control participants (de Boer et al., 2009).

c) Economic burden of cancer

Cancer also results in an economic burden for patients, countries, and society (Alzehr et al., 2022; Garcia Martin et al., 2022; Merollini et al., 2022; Park and Look, 2019). The economic burden of cancer includes healthcare expenditures (e.g., screening, diagnosis, and treatment costs), out-of-pocket expenditures (medical and non-medical), as well as expenditures related to morbidity (e.g., sick leave, work disability, and productivity losses) and premature death (mortality costs) (Jemal et al., 2019).

Today, the global economic cost of cancer is not clearly known. However, is thought to be in the hundreds of billions of dollars ($) per year (Jemal et al., 2019). A recent study, which projected the economic burden of 29 cancers in 204 countries and territories, revealed that the global economic cost of cancers between 2020 and 2050 is estimated at 25.2 trillion

international dollars (INT$) (S. Chen et al., 2023). This corresponding to an annual tax of 0.55% on global gross domestic product (GDP) (S. Chen et al., 2023). The authors highlighted that this cost varied widely according to cancer types and across countries. For example, of all cancers, tracheal, bronchus, and lung cancer have the highest economic cost with INT$3.9 trillion (15.4%) ; followed by colon and rectum cancer (INT $2.8 trillion, 10.9%); breast cancer (INT $2.0 trillion, 7.7%); liver cancer (INT $1.7 trillion,6.5%); and leukemia (INT $1.6 trillion, 6.3%) (S. Chen et al., 2023). With respect to regions or countries, the study also showed that North America has the highest cancer economic burden, with an annual tax of 0.83% of GDP followed by Europe and Central Asia (0.63%) and East Asia and the Pacific (0.59%) (S. Chen et al., 2023). The lowest cost is in Sub-Saharan Africa, at 0.24% of GDP (S. Chen et al., 2023).

Studies conducted in individual country confirm these results. In the USA, the economic burden of cancer is approximately 1.8% of the GDP (Jemal et al., 2019). The healthcare expenditure due to cancer were estimated at 161.2 billion US dollars (US$), the loss of productivity due to morbidity at US$30.3 billion dollars, and premature mortality at US$150.7 billion dollars (Jemal et al., 2019). An annual report indicated that the economic costs associated with cancer care for patients (aged over 18 years) were estimated to be US$21.09 billion in 2019, made up of patient out-of-pocket costs of US$16.22 billion and patient time costs of US$4.87 billion (Yabroff et al., 2021).

In Australia, a cohort study including 230,380 people diagnosed with a first malignancy found that the cumulative mean annual health expenditure (from 2013-2016) were 3.66 billion Australian dollars (AUD) (Merollini et al., 2022). The highest costs were incurred by patients with prostate cancer (AUD538 million), breast cancer (AUD496 million), and colorectal cancer (AUD476 million). Per capita, the overall mean annual healthcare costs were AUD15,889 and the highest costs per capita were for myeloma (AUD45,951), brain (AUD30,264), and liver cancer (AUD29,619) patients (Merollini et al., 2022).

In France in 2020, a report published by the French National Cancer Institute (INCa) showed that the economic cost of cancer increased by 48% between 2004 and 2017 (Asterès and Institut

National du Cancer, 2020). It has been reported that the cost of cancer, including healthcare expenditure, lost production costs due to morbidity, prevention, and research expenditure was estimated to be 18.3 billion euros (€) in 2017. The costs of productivity losses due to premature death amount to €9.7 billion, making the total cost of cancer at €28 billion (Asterès and Institut National du Cancer, 2020). The increase in the costs of cancer is due to the increase in the incidence and the reduction in the mortality rate. Similar results are reported in most developing countries, showing an increase in cancer costs.

In 2018, a population-based study conducted in BRICS countries (i.e., Brazil, Russia, India, China, and South Africa) by Pearce and colleagues showed that the total cost of productivity losses due to premature cancer death in these countries was US$46.3 billion, representing 0.33% of their combined GDP and equivalent to US$45,926 per cancer death (Pearce et al. 2018). The largest total productivity loss was in China (US$28 billion), while South Africa had the highest cost per cancer death (US$101,000) (Pearce et al., 2018).

In summary, the finding from various studies revealed that working-age cancer survivors experience a double challenge: first, they struggle with their health and the late adverse effects of treatment, second, they experience difficulties in returning to work, or are even likely to be unemployed. However, a better understanding of the RTW process in cancer survivors is necessary in order to propose appropriate interventions to mitigate the risk of long-term unemployment.

2. Return to work in cancer survivors

This section outlines a brief overview of the second thematic of the thesis: **"Return to work"** through a literature review. The section begins with the definition of the concept of RTW followed by its prevalence and importance for cancer survivors. Then, the determinants of RTW after cancer diagnosis and conceptual models of RTW are described.

2.1. Definitions of return to work

Although the term **"return to work"** is widely used in the field of occupational disability research, its definition remains elusive, making it difficult to understand (Young et al., 2005b).

To accurately assess the different outcomes associated with RTW, it is necessary to provide a clear definition of the different concepts relating to RTW, and to specify the most appropriate for studies involving cancer patients.

In the literature, two viewpoints emerged about the definition of RTW. RTW is utilized as both (i) an outcome measure and (ii) a dynamic process (Désiron et al., 2011). For many studies, it is defined as simple binary endpoint (Yes/No), meaning being or not being at work at a given point in time (e.g., the event of resuming work) (Butow et al., 2020; de Boer et al., 2015; Wasiak et al., 2007; Wells et al., 2013). As result, RTW is assessed as a characteristic of workers' employment status or experience (at work/not at work) (Young et al., 2005b). According to this definition, a wide variety of RTW outcome measures are presented in the literature. For example, in recent studies by Rosbjerb et al. (Rosbjerg et al., 2021) and Ullriche et al. (Ullrich et al., 2018), RTW is defined by work status at 12 months after sick leave assessed by one of the following options: "*being at work*" (without considering full time or part-time sick leave), or "*not being at work*" (including any kind of sickness absence compensation, permanent exit from the labor market) in the 12 months follow-up period. Moreover, De Rijk and colleagues differentiated between RTW defined as working again for the first time after reporting sick leave even when working fewer hours than indicated in the employee's contract, and sustainable RTW defined as RTW without recurrence during 13 months follow-up (Rijk et al., 2009). The definition of RTW as an endpoint is more static. It just aims to identify the patients who are at work and those who are out of work at given point after diagnosis. As such, many of the subtleties of the RTW process, such as the employment pathways beyond initial RTW, return to graduated duties, are not considered.

From these considerations, other definitions of RTW have been proposed. Thus, RTW is considered as a dynamic process taking into the entire employment trajectory after RTW (Young et al., 2005b). It was measured as (i) graduated RTW; (ii) working status and its nuances including the return to pre-diagnosis employer and/or job, attending a modified job (e.g., two days/week, RTW with modified hours/duties/role); and (iii) a variety of vocational outcomes definitions, including work capacity, work satisfaction, working hours per week, sustainable RTW (Greidanus et al., 2019; Porro et al., 2022b; Sheppard et al., 2019; Tiedtke et al., 2017; Tjulin et al.,

2010; Wasiak et al., 2007; Yarker et al., 2010; Young et al., 2005b). According to this approach, RTW is thought as a dynamic process (not as a dichotomous event) encompassing a series of events, transitions, and phases influenced by different factors (Wasiak et al., 2007). This definition represents a comprehensive view of RTW while including the entire period from the first hour of absence due to the health problem until the resumption of tasks that will be maintained in the long term (Wasiak et al., 2007).

In cancer research, de Boer and colleagues proposed a definition of RTW in cancer survivors taking this dynamic process into consideration (de Boer et al., 2015). Specifically, RTW is defined as a process that includes any work resumption (e.g., part-time, or full-time) to a previous job or a new job, either to the same role or reduced role following a sick leave period due to cancer (de Boer et al., 2015). In line with this approach, Porro and colleagues recently clarified the definition as follows: RTW can be defined as the process of returning to the same work situation in place pre-diagnosis after a full period of sick leave (with or without accommodation) (Porro et al., 2022b). According to these definitions, three distinct phases are identified in the RTW process: "*sickness absence*" (i.e., the worker is off work); *"work re-entry"* (i.e., the worker is back to work); and *"work retention"* (i.e., sustainability of work ability) (Tjulin et al., 2010; Young et al., 2005b). In **Table 4**, some terms related to RTW are presented.

Based on this brief overview, we noted that the definition of RTW vary widely in research. We also retained that RTW should not be considered merely as a state (dichotomous outcome), but also as a multi-phase process. The variation of RTW definitions should limit the generalizability of findings and their transfer to clinical practice (Knauf and Schultz, 2016). Similar observations have been highlighted in the reviews by Lamore and colleagues and Bilodeau and colleagues (Bilodeau et al., 2017; Lamore et al., 2019). For research on RTW and work retention in cancer survivors, the authors recommended clearly defining the RTW concept and how RTW after cancer diagnosis should be assessed (Bilodeau et al., 2017; Lamore et al., 2019). This will require a consensus from experts on RTW, employers, and cancer survivors to provide a clear basis for RTW research (Lamore et al., 2019). However, pending this work, we consider the

definition proposed by Porro et al. (Porro et al., 2022b) as the most appropriate for use in cancer research.

Table 4. Definition of terms related to return to work.

Term	Definition
Sickness absence	begins the first day of sick leave due to a health problem and ends when the RTW phase begins.
Return to work	refers to the action of resuming work after the onset of a disability and in particular a chronic disease (generally at the end of a more or less long period of sick leave)
Sustainable RTW (Work retention)	defined as a stable full-time or part-time RTW to either the original or a modified job for a long-term period (i.e., at least 28 days or 3 months), without relapse or sickness absence re-occurrence (Endo et al., 2018; Etuknwa et al., 2019; van Egmond et al., 2016).
Time to RTW	is the time (i.e., duration in days, months, and years) between the first day of sick leave and the first day of work resumption (either part-time or full-time). It begins the first day that the worker returns to the workplace to perform a job (the same as before the absence, with modified tasks or as part of a progressive return).

Source: adapted from definition proposed by Young et al. (Young et al., 2005a).

2.2. Importance of work for cancer survivors

Work constitutes an essential component of self-identity and self-esteem; provides financial security; establishes and maintains social relationships; and represents an individual's abilities, talents, and health (Lilliehorn et al., 2013; van der Noordt et al., 2014; Wells et al., 2013). As such, it is of great importance for cancer patients. Several studies have shown that returning to work or re-employment is very important for cancer survivors, their families, and society (Amir et al., 2008; Chen et al., 2021; Kennedy et al., 2007; Lilliehorn et al., 2013). For example, most cancer survivors regard RTW as a symbol of completed recovery and regaining a normal life (Banning, 2011). RTW largely contributes to cancer survivors' rehabilitation, improve their HRQoL and self-esteem (de Boer et al., 2015; Park and Shubair, 2013), and ensures their financial security by providing necessary income (Duijts et al., 2017; Jeong et al., 2019).

For families, RTW can help maintain family income, family cohesion, give a sense of meaning, and health (Jeong et al., 2019). From a societal perspective, it is an economic and social imperative to encourage patients to RTW whenever possible, because employment provide a social connection and reduces the productivity losses due to cancer (de Boer et al., 2008; Luengo-Fernandez et al., 2013; Shakespeare, 2018).

2.3. Prevalence of return to work in cancer survivors

Given the importance of work for cancer survivors, it is essential to gain an overview of the proportion of cancer survivors who manage to work or fail RTW after a diagnosis. Here, we present the results of some studies to illustrate these issues.

In 2011, a meta-analysis by Mehnert et al. (Mehnert, 2011) estimated the overall prevalence of RTW among cancer survivors at 63.5%, after a mean duration of absence from work of 151 days. However, the authors indicated that the prevalence varies depending on the period after cancer diagnosis. They found that, at 6 months following diagnosis, an average 40% of patients had returned to work or had continued working during treatment, at 12 months a mean of 62% had returned to work, at 18 months a mean of 73% had returned to work, and at 24 months an average 89% of patients had returned to work (Mehnert, 2011).

The prevalence also varies according to the type of cancer and across countries. A systematic review and meta-analysis by Tavan and colleagues showed an overall rate of RTW at 72%, for all cancer locations (Tavan et al., 2019). The rate of RTW in Asia and Europe was 57% (range 50-65%) and 52% (range 43-60%), respectively (Tavan et al., 2019). Another systematic review from North-Western and Central European countries, including 12 population-based studies found rates of RTW for cancer survivors in Europe that ranged from 39% to 77%, with an average of 64% (Paltrinieri et al., 2018). The median duration of RTW was 2 years (Paltrinieri et al., 2018). In Taiwan, a retrospective cohort study among employees with an initial diagnosis of cancer showed that 70.4% remained employed through the first year after the diagnosis of cancer (Chen et al., 2021). Patients with cervical cancer (86.1%), female breast cancer (83.6%), and thyroid cancer (82.6%) represented the highest proportion of cancer survivors who remained employed one year after cancer diagnosis (Chen

et al., 2021). These results are consistent with those reported in a study conducted in Germany which showed that almost 74% of cancer survivors (all type of cancer) have returned to work one year after cancer diagnosis (Lieb et al., 2022). The study also revealed that slightly more men (77%) returned to work than women (72%) and that rates of RTW significantly differed by type of tumor, treatment modality, and metastases (Lieb et al., 2022).

In France, few studies to our knowledge have investigated the RTW rates in cancer survivors, with the majority focusing on breast cancer (Fantoni et al., 2010; Guittard et al., 2016; Peugniez et al., 2011; Rolland et al., 2023). In 2010, the study by Fantoni et al. (Fantoni et al., 2010) which surveyed 379 women with breast cancer aged 18-60 years found that 82.1% of women who had worked at the time of the diagnosis returned to work after a median sick leave of 10.8 months. One year later, the study of Peugniez and colleagues reported similar results (Peugniez et al., 2011). They found that 80% of the patients returned to work after a median delay of 11.5 months of sick leave (Peugniez et al., 2011). More recently, a study of 303 breast cancer patients found that 73% of women returned to work within 2 years after diagnosis (Rolland et al., 2023). It is also showed that the time to RTW was significantly longer in women who received chemotherapy (Rolland et al., 2023). In the long term (i.e., over 2 years), the rate of RTW seems relatively constant, ranging from 80 to 90%. The study by Guittard and colleagues reported a 3-years RTW rate of 91% in breast cancer survivors, with a median sick leave duration of 410 days (Guittard et al., 2016). Furthermore, in 2018, the VICAN 5 survey, which included 4174 participants diagnosed with cancer (12 cancer sites), revealed that 80% of patients aged between 18 and 54 years and employed at diagnosis were still employed five years later (Rivière, 2018). The analysis by cancer location showed a lower rate of RTW in lung cancer patients, followed by upper aerodigestive tract (UADT), colorectal, kidney, and prostate cancers (Rivière, 2018).

Although most cancer survivors are able to RTW after cancer diagnosis or treatment, some have difficulty maintaining sustainable employment after RTW (Duijts et al., 2017). For instance, in a study of 1,033 Japanese male cancer survivors, 786 employees (76.1%) returned to work after their first episode of sick leave due to cancer (Endo et al., 2018). Work retention rate among all subjects were 80.1% one year after RTW. However, this percentage dropped to

49% after 5 years. The authors concluded that work retention rates vary significantly with cancer type, with the lowest work retention rates after initial RTW in survivors of lung, liver, pancreas, and esophageal cancer (Endo et al., 2018). In addition, findings from a recent systematic review involving 14,207 cancer survivors showed that the pooled prevalence of long-term work retention was 73% 2 years after diagnosis (de Boer et al., 2020). The study indicated that, as time from diagnosis increased, the rate of work retention decreased. However, the rate of remaining at work between 2 and 2.9 years was 72%; between 3 and 3.9 years, 80%; between 4 and 4.9 years, 75%; between 5 and 5.9 years, 74%; and between 6 years and more, 65% diagnosis (de Boer et al., 2020).

Findings from the above studies show that a proportion of cancer survivors cannot RTW and many may not last in their jobs beyond initial reintegration into the workplace (Zegers et al., 2021). Several factors have been identified as influencing RTW outcomes in cancer survivors (Islam et al., 2014). Understanding the RTW experience of cancer survivors, and particularly factors that impede it; enables early detection of patients at risk of barriers to RTW, and to provide appropriate supportive interventions. In the following section, we described the determinants of RTW after cancer diagnosis.

2.4. Determinants of return to work in cancer survivors

In the last decade, the determinants of RTW in cancer survivors have been widely described (Arfi et al., 2018; Giuliani et al., 2019; Porro et al., 2022b). In the literature, several factors have been identified as being associated with the RTW among cancer survivors (Colombino et al., 2020; Islam et al., 2014; Paltrinieri et al., 2018; Ross et al., 2012; Zhang et al., 2022). These factors were grouped into facilitators (positive impact) and barriers (negative impact) (Hallgren et al., 2022; Marinas-Sanz et al., 2023; van Maarschalkerweerd et al., 2020) and categorized into three main factors according to whether they are related to the patient (socio-demographic factors), the disease (disease and treatment factors), or to the work (work-related factors) (Colombino et al., 2020). **Table 5** presents a summary of the different factors (facilitators and obstacles) associated with RTW after cancer diagnosis according to each category

Table 5. Synthesis of determinants of return to work.

Socio-demographic factors (personal characteristics)	
Facilitators	**Barriers**
• Younger age 35-49 years • Men • Support from family and relatives • High income • High education level • Marital status: no spouse/single, widow, or divorced	• Older age (>50 years) • Women • Low level of education • Low household income • Ethnicity: black race
Disease and treatment-related factors	
Facilitators	**Obstacles**
• Early tumor stage • Smaller initial tumor size • Breast cancer, • Radiotherapy • Non-use of adjuvant therapy • Lower physical and psychological symptoms	• Advanced tumor stage • Lung; brain; head and neck cancers • Chemotherapy, extensive surgery • Combination of therapies • Multiple co-morbidities • Lymphedema, fatigue, pain. • Anxiety, depression, emotional distress, and cognitive impairment
Work-related or professional factors	
Facilitators	**Obstacles**
• Self-employment • Flexible work arrangements: accommodation or adjustments of workplace, flexibility in work hours • Support from employer, supervisors, managers, and colleagues • Collaboration with social welfare service • Favorable labor law or supportive legislative • No universal health care insurance	• Time constraints • Working in the private sector and small-sized companies • Lack of support from supervisors and colleagues • High physical work demands: heavy physical work, heavy lifting work, manual labor • Discrimination related to cancer in workplace • Early or longer disability pension • High health insurance coverage

Source: adapted from Islam et al. (Islam et al., 2014) and Kiasuwa-Mbengi et al. (Kiasuwa-Mbengi et al., 2016).

The factors summarized in the table are briefly described in the subsections below.

2.4.1. Socio-demographic factors

Personal characteristics such as age, gender, education level, income, ethnicity, marital status, and the existence of relationship with surrounding people have been identified to influence the likelihood of returning to work (Islam et al., 2014). As such, younger age, higher education, marital status single, divorced or widowed, and support from friends and family have been reported as key facilitators of RTW and continue work (Caumette et al., 2021; Fantoni et al., 2010; Marinas-Sanz et al., 2023; Tamminga, 2012; Tsai et al., 2022). On the other hand, being female and/or older (over 50), as well as a low income and low level of education represent a higher risk for falling out of work (Marino et al., 2013; Mehnert, 2011). For example, a review of 43 qualitative and quantitative studies, supplemented by an expert consultation, found that for both female and male cancer survivors, age over 50 and 55 years, respectively, was associated with an increased risk of delayed RTW or early retirement (Kiasuwa-Mbengi et al., 2016). Moreover, the study by Blinder and colleagues showed that the African-Caribbean and Malay ethnic groups (black race) receive better support from their friends and family, which then positively affects their decision-making to RTW (Blinder et al., 2012).

2.4.2. Disease and treatment-related factors

The cancer and treatment-related factors that have impact on RTW include type and stage of cancer, type of treatment, physical fitness level, and co-morbidities, among others (Islam et al., 2014; Ross et al., 2012). For instance, early cancer diagnosis (early stage) and smaller initial tumor size have been reported as an important facilitator for RTW (Cocchiara et al., 2018; Colombino et al., 2020). A review by Van Muijen et colleagues including 28 cohort studies of all working-age cancer survivors, aged between 18 and 65 years showed that the breast cancer survivors had the greatest chance of RTW (van Muijen et al., 2013). Advanced stages of cancer; types of cancer such as lung, head and neck, stomach, leukemia, and central nervous system cancers; and other associated comorbidities are identified as barriers to re-employment (Kiasuwa-Mbengi et al., 2016; Paltrinieri et al., 2020; Porro et al., 2022b; Ross et al., 2012; Taskila and Lindbohm, 2007; Zhang et al., 2023). Regarding treatment modalities, chemotherapy, extensive surgery, and the combination of multiple therapies were found to be important barriers to RTW (Ahn et al., 2009; Fantoni et al., 2010; Kiasuwa-Mbengi

et al., 2016; Rollin et al., 2019; van Muijen et al., 2013). Specifically, two recent studies conducted in France found that chemotherapy was significantly associated with a longer duration of sick leave in breast cancer survivors (Arfi et al., 2018; Rolland et al., 2023). Other studies reported that cancer survivors who had extensive surgery (i.e., mastectomy and axillary node dissection) or a combination of therapies (e.g. surgery, radiotherapy, and chemotherapy) had a fourfold increased risk of not resuming work in the first years after treatment, compared to cancer survivors who had only surgery or one type of treatment (de Boer et al., 2008; Kiasuwa-Mbengi et al., 2016). The various treatment modalities lead to several side effects, such as pain, lymphedema, fatigue, anxiety, depression, and cognitive impairment, which act as barriers to RTW (Islam et al., 2014; Kiasuwa-Mbengi et al., 2016).

2.4.3. Work-related factors

The type of job the cancer survivor is engaged in, and the work environment can affect their ability to RTW and remain employed (Islam et al., 2014). Manual work, heavy physical work, and working in the private sector are identified as barriers for RTW (Colombino et al., 2020; Kiasuwa-Mbengi et al., 2016). It was also shown that cancer survivors in blue-collar occupations are less likely to RTW compared to those who have white-collar jobs such as office work (Lindbohm et al., 2012; Rangabashyam et al., 2021; Zhang et al., 2023). Moreover, a qualitative study (with semi-structured, recorded interviews) based on 35 breast cancer survivors identified the high physical demands at work, lack of support from colleagues and employers, and time constraints as factors that negatively affect RTW of cancer survivors (Sun et al., 2016).

In contrast, self-employment; the accommodation of the workplace; and support from employers, supervisors, and colleagues were identified as key facilitators od RTW (Kiasuwa-Mbengi et al., 2016; Marinas-Sanz et al., 2023; Sun et al., 2016; Taskila and Lindbohm, 2007). For example, perceived employee accommodations in the form of taking illness into consideration when planning and managing the work tasks are strong and significant positive predictors for RTW (Mehnert, 2011; Mehnert and Koch, 2013; Steiner et al., 2010). Besides, self-employment; workplace adjustments or accommodation (e.g., having shorter or flexible working hours, working from

home, less manual job, etc.); and positive and active support from employers and colleagues are reported to be positively associated with RTW (Landeiro et al., 2018; Tamminga, 2012).

Lastly, the healthcare system, the national health insurance system, labor policies and social welfare system are also essential factors that can have major influences on RTW process (Chow et al., 2014; Cocchiara et al., 2018; Kiasuwa-Mbengi et al., 2018). Living in a country with an universal health care insurance system or subscribing to individual health insurance can significantly influence the decision to resume employment after cancer treatment (Ross et al., 2012). For example, countries that do not have universal health care insurance, like the USA, cancer survivors are more likely to RTW compared to western countries because of the fear of losing health insurance as most of worker have access to health assurance via their employer (Wang et al., 2018). A study by Hasset et al. (Hassett et al., 2009) showed that 93% of insured women return to their work within 12 months after diagnosis in the USA. In addition, a Chinese study which included 396 patients showed that cancer survivors with higher insurance coverage were four times more likely to extend their sick leave period compared to those with lower medical insurance coverage (Li et al., 2021). In the literature review by Kiasuwa-Mbengi et al. (Kiasuwa-Mbengi et al., 2018), collaboration between health care personal, the social welfare service, and employers have been reported to be effective and required to achieve successful reintegration to work. A study from Taiwan, pointed out that beneficial welfare policies (disability pensions) could reduce the financial burden of patients, which could potentially motivate them to retire earlier rather than overcome challenges to RTW (Chen et al., 2019). Labor market laws or employment policies that promote job retention or work reintegration for people with chronic disease (e.g., cancer) are also shown to be facilitators of RTW (Silvaggi et al., 2020).

2.5. Return to work of cancer survivors: explanatory conceptual models

Several conceptual models have been suggested in the literature to explain the relationship between different factors and how they interact to influence RTW (Amir et al., 2009; Feuerstein et al., 2010; Loisel et al., 2001; Mehnert, 2011; Porro et al., 2022b; Steiner et al., 2004; Wells et al., 2013).

These models provide a framework that can help healthcare professionals (HCPs) and researchers in understanding the process of returning to work after sick leave (Feuerstein et al., 2010). We describe below three models that seem appropriate to our research object (Feuerstein et al., 2010; Loisel et al., 2001; Porro et al., 2022b).

2.5.1. The Arena of Work Disability Prevention model

In 2001, Loisel and colleagues was created the "**Arena of Work Disability Prevention model**" **(WDP Arena model)** to better define and elucidate the contextual factors of work disability prevention (Loisel et al., 2001). The model was originally developed to identify barriers and facilitators in the process of returning to work following an episode of low back pain, and to understand the complexity of the process (Six Dijkstra et al., 2023). Loisel et al. (Loisel et al., 2001) acknowledge RTW as a multifactorial process situated in an arena of multiple integrating systems grouped into four specific systems: (i) *personal*, (ii) *workplace*, (iii) *healthcare*, and (iv) *the legislative and insurance systems* and 2 general systems (1) *overall societal context* and (2) *culture and politics* that are all important for RTW (Costa-Black et al., 2013; Loisel et al., 2001). Through illustrating various systems, this model maps the relevant factors and systems that need to be incorporated into work disability prevention programs (Ståhl, 2010). The model also clarifies the importance of situating research within the specific societal context in which the intervention is intended; thus, the model needs to be adapted and altered in order to be useful in another context. The WDP Arena was principally developed for industrial workers with disability due to low back pain (Loisel et al., 2001) and was later adapted for all musculoskeletal disorders (Loisel et al., 2005; Six Dijkstra et al., 2023; Skamagki et al., 2022). It has also been applied to RTW in patients with other chronic diseases, such as cancer survivors and workers with occupational injuries in general (Fassier et al., 2015; Greidanus, 2021; Six Dijkstra et al., 2023; Szeto et al., 2011; Tamminga et al., 2019). **Figure 3** presents the adapted form of the Arena model proposed by Greidanus et al. (Greidanus, 2021), in which " workers with disability from musculoskeletal pain" in the center is replaced by "cancer survivor".

Although the Arena model is widely used, it has been criticized in a recent study by Sun and colleagues who pointed out that the model did not include some cancer-specific factors such as lymphedema or the specific side effects of certain adjuvant treatments (Sun et al., 2017). According to the authors, the inclusion of these factors in the model may be essential to understanding the entire process of RTW (Sun et al., 2017).

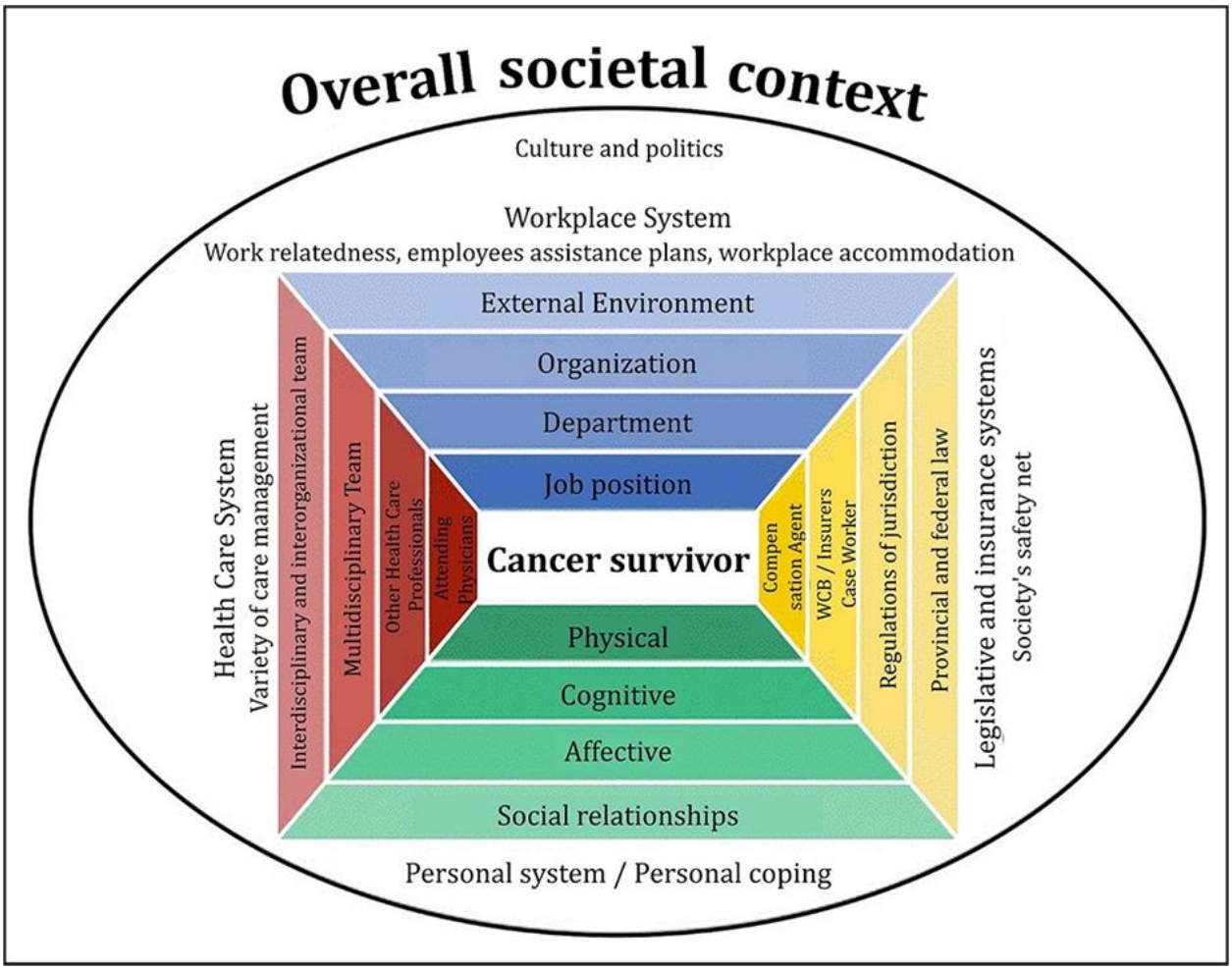

Figure 3. The Arena of work disability model.

Source: adapted from Greidanus et al. (Greidanus, 2021; Loisel et al., 2001) and Loisel et al. (Greidanus, 2021; Loisel et al., 2001).

2.5.2. The model Cancer and Work

Further, in order to illustrate the multidimensional factors that can influence various work outcomes among cancer survivors, Feuerstein and colleagues developed **"Cancer and Work model"** (Feuerstein et al., 2010). This model was developed from a systematic review and completed by the literature related to cancer and work. The authors included information from qualitative studies, case examples, and clinical experiences. The development was based on

the different types of existing models: biomedical, psychosocial, psychiatric, ecological, economic, and biopsychosocial models (Leibowitz, 1991; Leyshon and Shaw, 2008; Schultz et al., 2007; Turk, 1996; WHO, 2001). Therefore, the model is composed of seven categories of determinants that may influence RTW after cancer: (1) *cancer survivor characteristics*, (2) *health and well-being,* (3) *symptoms,* (4) *function* (e.g., current level of function or functional status such as strength, flexibility, aerobic capacity), (5) *work demands*, (6) *work environment*, and finally (7) *factors associated with policies, procedures, and economics* (Feuerstein et al., 2010). The model proposes that all these factors, in combination with one another, influence various outcomes associated with returning to work: RTW itself, work ability, work performance, and work retention (Feuerstein et al., 2010). **Figure 4** illustrates the clinical model with the seven broad categories of factors associated with the four outcomes indicated above. One of the main strengths of the model is its comprehensive multi-system approach (Caron, 2020). It provides a comprehensive conceptualization of cancer survivorship and work, including all the major factors that can influence the process of RTW and job retention (Islam et al., 2014; Moskowitz et al., 2012). In addition, it was developed to be used by researchers and clinicians as a guide for dealing with RTW in cancer survivors (Feuerstein et al., 2010). Therefore, the model has been used in a few qualitative studies on RTW after cancer to guide data collection (Horsboel et al., 2012) or the organization of results (Kiasuwa-Mbengi et al., 2019). The authors point out that the relationships (directional and bidirectional) among categories are not exhaustive (Feuerstein et al., 2010). Others certainly are possible. In addition, they emphasize that despite the linear appearance of the model, it is possible that non-linear relationships may exist as well. Finally, the model is generic for all types of cancer, and some symptoms, such as lymphedema, are not included even if they are common in breast cancer survivors (Caron, 2020). Feuerstein et al. (Feuerstein et al., 2010) concluded that there is a need to develop effective and efficient cancer-specific approaches that identify and target the areas related to the many dimensions of work disability in cancer patients over the course of the illness.

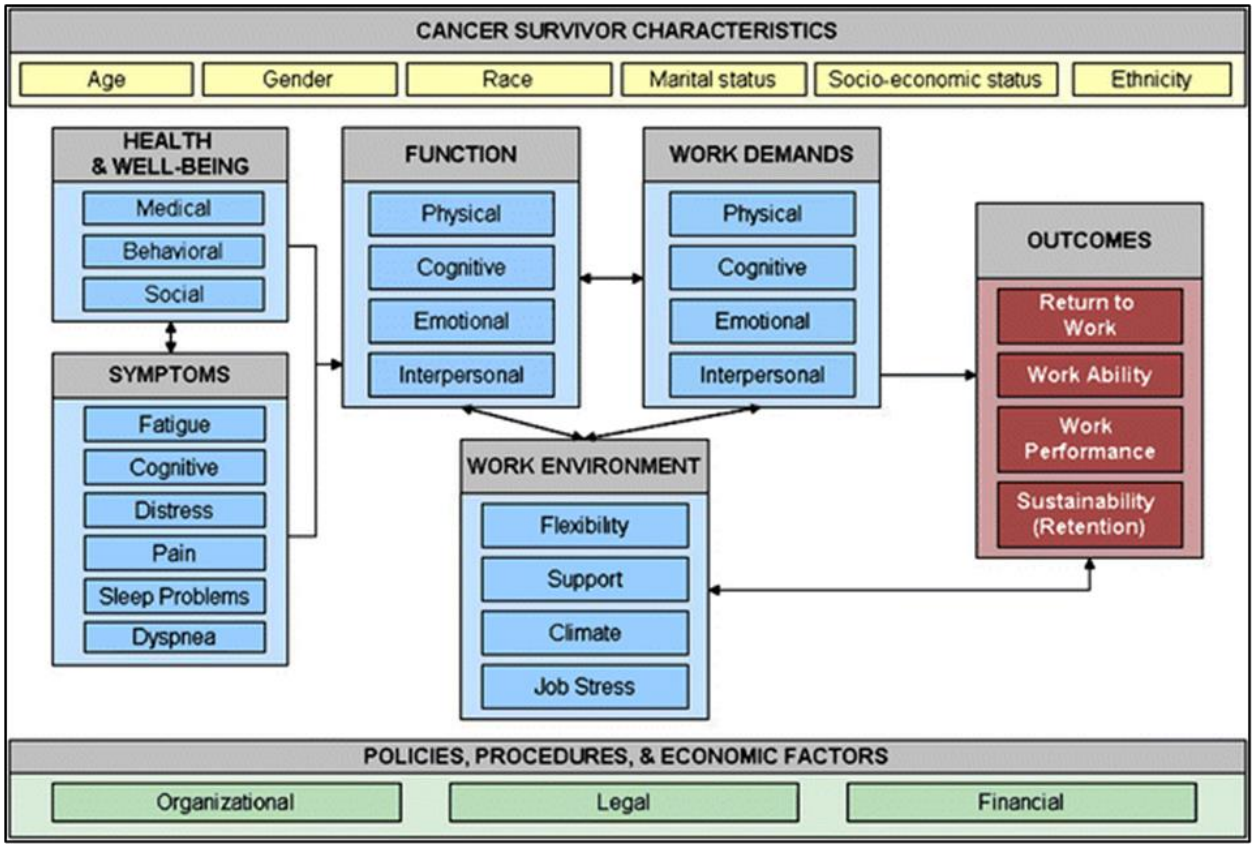

Figure 4. Cancer and work model. From Feuerstein et al. (Feuerstein et al., 2010).

2.5.3. The model of return to work of breast cancer survivors

To address gaps identified in the previous models, Porro et colleagues have recently proposed an integrative transactional conceptual model of the RTW for breast cancer survivors (**the REWORK-BC model**) (Porro et al., 2022b). The REWORK-BC model was designed specifically to explain the RTW process of women diagnosed with breast cancer according to the transactional approach (Porro et al., 2022b). It has been developed following a systematic review and expert consensus method. First, the authors identified a list of 62 determinants associated with the RTW of breast cancer survivors through a systematic review. Then, the determinants were validated by TRIAGE[3] methods (Albert et al., 2014) and grouped into four broad categories:

[3] **TRIAGE** or Technique for Research of Information by Animation of a Group of Experts is a a qualitative method in which participants must, through discussion, sort statements to obtain a group consensus on a given subject (Gervais & Pépin, 2002). It is an inductive and structured method for collecting information comprised of a series of formal, successive steps that aims to reach a group consensus.

(1) *breast cancer characteristics*, (2) *primary appraisal* (work ability), (3) *secondary appraisal* (resources), and (4) *adjustment strategies* (see **Figure 5**).

The main advantage of this model is that it combines evidence from systematic reviews with expert knowledge (de Boer et al., 2023) and is focused on a specific cancer site (breast cancer). In addition, the direct and indirect relationships between determinants have been clearly explained. Finally, the REWORK-BC integrates several systems (from the WDP Arena model) making it generalizable: (i) the individual system specific to the breast cancer characteristics and perceptions, (ii) the hospital system including the role of HCPs, (iii) the occupation systems (i.e., the role of managers and colleagues), and (iv) the financial system (Porro et al., 2022b). However, the model could be adapted to other types of cancer by modifying the breast cancer-specific characteristics. While the REWORK-BC model is most appropriate for cancer survivors, it represents several hypotheses that need to be supported and validated in patients through clinical studies.

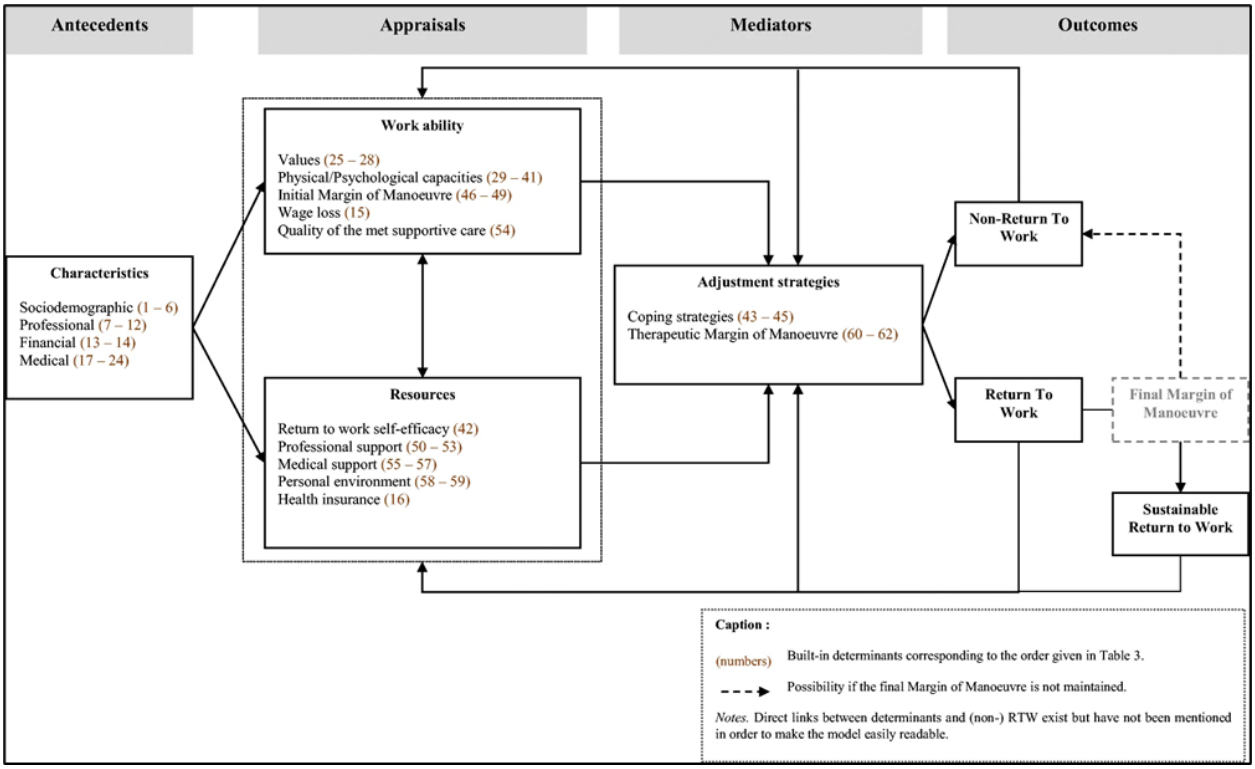

Figure 5. An integrative transactional conceptual model of the RTW of breast cancer survivors (REWORK-BC model). From Porro et al. (Porro et al., 2022b).

3. Physical activity

In this section, we focus on the third thematic of the thesis, **"Physical Activity"**. First, AP and its various relative terms are defined. Then, based on data from the literature, characteristics and measurement methods of PA are described.

3.1. Definition of physical activity

In the field of PA and cancer research, as well as in clinical settings, the terms PA, exercise, and physical fitness are commonly used. However, when mentioned in studies, it is often difficult to distinguish these terms. In fact, they are often used interchangeably and are subject to misunderstandings and different interpretations, which leads to confusion. Therefore, we provide a clear definition of these concepts to prevent confusion about their use in this thesis.

The most popular and widely used definition of PA was published by Caspersen and colleagues in 1985 (Caspersen et al., 1985). They defined PA as "*any bodily movement produced by skeletal muscles that results in an increase in energy expenditure above the resting energy expenditure (basal levels)*" (Caspersen et al., 1985). It includes all movements performed in daily life and is not limited to leisure or sports activities. According to the context, the PA is categorized into four major subgroups which are: (1) household or domestic activities, (2) transportation activities (i.e., activity performed to get to and from places), (3) occupational activities, and (4) recreational or leisure-time activities (including sport and physical exercise) (Bull et al., 2020; Caspersen et al., 1985; Khan et al., 2012).

Exercise is defined as *"planned, structured, and repetitive bodily movement, aimed at improving or maintaining physical fitness"* (Caspersen et al., 1985). It constitutes all or part of the category of leisure-time activities. As such, exercise is not synonymous with PA, but a subset of PA. Physical exercise is generally classified according to the physiological functions to be developed or improved (e.g., cardiorespiratory, neuromuscular, flexibility, etc.). Therefore, the different types of exercise are aerobic exercise, resistance exercise, flexibility exercise, and balance exercise (Caspersen et al., 1985; WHO, 2010). Specifically, according to the

American College of Sports Medicine (ASCM), aerobic or endurance exercise refers to any activity that engages major muscle groups and causes the body to use more oxygen than at rest (e.g., walking, jogging, running, cycling, dancing, skating, swimming, household chores, etc.) (Ferguson, 2014). The goal of aerobic exercise is to increase cardiovascular endurance (Wilmore and Knuttgen, 2003). The resistance exercise, also called strength training, refers to any activity that primarily involves the musculoskeletal system and requires a muscle or muscle groups (e.g., hamstrings, hip adductors/abductors, upper/lower back, abdomen, chest, shoulders, biceps/triceps, or neck) to work against an external resistance, such as pull-ups, dumbbells, or elastic bands (Ferguson, 2014). It strengthens and tones muscles, as well as improves bone density, balance, and coordination. Flexibility or stretching exercise refers to activities that elongate muscles to increase the range of motion around the joints. These activities can be static (i.e., holding the stretch for a certain amount of time), dynamic (i.e., a fluid movement, such as tai chi), or active (such as yoga). These types of exercise can be used alone or in combination in PA programs for cancer patients (Ferguson, 2014). **Table 6** presents the summary of the different types of PA with operational definitions and examples.

Finally, **physical fitness** has been defined as *"the ability to carry out daily tasks with vigor and alertness, without undue fatigue* (Caspersen et al., 1985), *and with ample energy to enjoy leisure time pursuits and to meet unforeseen emergencies"* (Clarke, 1971). According to Caspersen and colleagues, physical fitness refers to a set of attributes that people have or achieve that relates to the ability to perform PA (Caspersen et al., 1985). The health-related components of physical fitness are (a) cardiorespiratory endurance, (b) muscular endurance, (c) muscular strength, (d) body composition, and (e) flexibility (Caspersen et al., 1985).

In general, these definitions serve as a framework for understanding health studies and scientific reports related to PA, exercise, and physical fitness. Specifically, it will facilitate understanding and interpretation of findings of the thesis.

Table 6. Definition of physical activity and its related terms.

Types of physical activity	Definition	Example
Physical activity (PA)	Any bodily movement produced by skeletal muscles that result in energy expenditure, which can be measured in kilocalories (as energy expenditure).	PA includes daily life activities: transportation, work-related activities, performing household activities, exercising, and engaging in sports activities.
Household PA	PA undertaken in the home for domestic duties.	Cleaning, caring for children, gardening, etc.
Transportation PA	PA performed for the purpose of getting to and from places, and refers to the use of non-motorized means of locomotion with wheels, such as scooters, rollerblades, manual wheelchairs, etc.	Walking, cycling, Riding a scooter or roller skates.
Occupation PA	PA undertaken during paid or voluntary work.	Manual labor tasks, walking, carrying, or lifting objects
Leisure PA	PA performed by an individual that is not required as an essential activity of daily living and is performed at the discretion of the individual.	Examples include sports participation, exercise conditioning or training, and recreational activities such as going for a walk, dancing, and gardening.
Exercise	Form of PA that is planned, structured, repeated and has a final or an intermediate objective to the improve or maintain physical fitness and health.	Aerobic, resistance, flexibility, and balance exercises.
Aerobic or endurance exercise	Any activity that uses large muscle groups and causes your body to use more oxygen than it would while resting. It causes a person's heart to beat faster, and they will breathe harder than normal. It improves cardiorespiratory fitness.	Running, swimming, dancing, brisk walking, jogging, and bicycling.
Resistance or strength exercise	Also called strength training (muscles and bone strengthening), it is a PA primarily designed to firm, strengthen, and tone muscles, as well as promote bone growth and strength.	Examples include any type of jumps, lifting weights, bicep curls, shoulder presses, bench presses, barbell squats, pushups, lunges, pelvic floor muscle training, and bent-over rows.
Flexibility or stretching exercises	Flexibility exercises stretch muscles and can help the body stay flexible. These activities help to improve joint flexibility and keep muscles limber, thereby preventing injury.	Yoga, Tai chi, and Pilates
Balance exercise	Static and dynamic exercises are designed to improve an individual's ability to withstand challenges from postural sway or destabilizing stimuli caused by self-motion, the environment, or other objects.	Walking backward, standing on one leg.

Source: adapted from WHO 2020 guidelines on PA and sedentary behavior (Bull et al., 2020).

In this thesis, the use of the term "physical exercise or exercise" refers to PA categories from the American College of Sports Medicine guidelines (e.g., aerobic exercise, resistance, stretching, endurance, strength training, flexibility, or combinations of these exercises) (American College of Sports Medicine, 2021).

3.2. Characteristics of physical activity

All types of PA are characterized by four parameters: frequency, intensity, time (duration), and type (FITT), allowing to estimate the exercise dose (Barisic et al., 2011). These four components constitute the foundation of PA or exercise prescription, referred to as the FITT principle (Thompson et al. 2010). Therefore, in clinical practice, the prescription of PA should be likened to a medication prescription that details the appropriate type, frequency, intensity, and duration of exercise (Winters-Stone et al., 2014). The descriptions of the FITT characteristics of PA in clinical setting are summarized in **Table 7** (Thompson et al., 2010; Torregrosa et al., 2022).

Table 7. The characteristics of PA and its signification.

Term	Description
Frequency (F)	It captures the number of exercise sessions performed during a period (e.g., 3 or 5 sessions of PA/day).
Intensity (I)	How hard or strenuous to do a single bout of exercise corresponding to the energy expenditure induced during the exercise. Metabolic equivalent of Task (MET) is a unit used to express exercise intensity, as ml per kg per min of oxygen being consumed (Pate et al., 1995). It is a standardized program derived from the Compendium of PA[4]. 1 MET (3.5 ml O2/Kg/min) is the rate of energy expenditure while sitting at rest. MET allows to classify the PA into 4 levels according to intensity: Light or low intensity exercise is an activity done at 1.6 to 2.9 METs Moderate intensity exercise is an activity done at 3 to 5.9 METs Vigorous or high exercise is an activity done at ≥ 6 METs.
Time (T)	The length of time (duration) in which a single bout of activity or exercise is performed. It is generally expressed in minutes or hours (e.g., 45 min of exercise per session).
Type (T)	The modality of exercise performed. For example, aerobic exercises like walking, jogging, biking, swimming, dancing, or strengthening activities such as exercises using exercise bands, weight machines, or hand-held weights, etc.
Dose of PA	It refers to the total amount of exercise performed over a given period (usually per week), or over the course of an extended exercise program. It is estimated as a function (product) of the frequency, intensity, and duration (time) of the exercise performed, and expressed in (MET-hour/week) (Wasfy and Baggish, 2016).

Source: adapted from Strath et al. (Strath et al., 2013).

[4] The adult Compendium of Physical Activities was developed for use in epidemiologic studies to standardize the assignment of MET intensities in physical activity questionnaires (Ainsworth et al., 2011). It has been used in studies worldwide to assign intensity units to physical activity questionnaires and to develop innovative ways to assess energy expenditure in physical activity studies.

3.3. Measurement of physical activity

PA is increasingly studied in epidemiological research (Lagerros and Lagiou, 2007). However, studies are often hampered by the difficulty of using valid and reliable tools to measure PA. In this section, the various tools used to assess PA are briefly presented.

There are two broad categories of methods available to assess PA: subjective methods and objective methods (Strath et al., 2013). Subjective methodologies rely on the individual either to record activities as they occur or to recall previous activities (self-reported measures). Objective methodologies include all wearable monitors that directly measure one or more bio-signals, such as acceleration, heart rate, or some other indicator of PA or energy expenditure, as they occur (Strath et al., 2013). In observational and interventional studies, the most frequently tools used are based on declarative data (collected by questionnaires, diaries; logs; recalls, or interview) (Sallis and Saelens, 2000), and more rarely on objective measurements of PA from dedicated and validated devices (e.g., pedometer, accelerometer, heart rate monitor) (Ancellin and Gaillot-de Saintignon, 2017). Self-reported questionnaires are frequently used to assess PA in both clinical care and research settings because they are simple (easily administered), relatively inexpensive, involve minimal time investment, and participant burden (Granger et al., 2015). However, there are numerous limitations to self-reported methods, which include: difficulties in ascertaining the frequency, duration, and intensity of PA, capturing all domains of PA, social desirability bias and the cognitive demands of recall (recall bias) that are likely to over- or underestimate PA levels (Sallis and Saelens, 2000). In contrast, the use of monitors, or accelerometers, to assess PA provides an objective comprehensive assessment of daily free-living PA across multiple levels of exertion (Plasqui and Westerterp, 2007). Unfortunately, accelerometer assessments are expensive and labor intensive because they have to be initialized before and read out after use, followed by data processing and analysis (Wright et al., 2017).

Although various measurement methods are available to assess PA, there is no gold standard for measuring PA in daily life on a large scale. In addition, the heterogeneity of methods and their implementation in studies constitute a barrier for the comparability of studies. However,

the choice of a methods should depend on several factors such as the endpoint of the study, the study population, and the outcomes of the questionnaire (Pols et al., 1998). The most accurate and fairest approach to measuring PA should be based on a combination of objective methods (using dedicated equipment and materials) with declarative methods (Ancellin and Gaillot-de Saintignon, 2017). They represent an advantage in reducing reporting bias.

Synthesis of chapter 2

This second chapter allowed to establish our research object through an extensive state-of-the-art on the three main concepts of the thesis: cancer, PA, and RTW after a cancer diagnosis.

In summary, cancers are a large group of diseases which can be caused by multiple factors (i.e. external and internal factors) and occur in any organ or tissue of the body. There are several treatment modalities for management of cancers that have contributed to the increase of cancer survival. Moreover, we highlighted that cancer, and its treatments have several adverse effects which negatively impact the QoL of cancer survivors. They are also associated with economic burdens for countries, society, and individuals and negatively impact the work-life of cancer survivors. A better understanding of all these difficulties will enable HCPs and researchers to develop appropriate management strategies to address them and support the RTW of cancer survivors.

Furthermore, the state of the art on RTW allowed to understand that RTW after cancer diagnosis is a complex and multifactorial process, influenced by a wide range of factors. The conceptual models also enabled a better understanding of the issues related to RTW among cancer survivors. These understandings are useful for better planning of interventions to support cancer survivors in RTW process. Lastly, we describe PA, which was been shown to be one of the major supportive care programs for improving the vocational rehabilitation of cancer survivors.

In the next chapter, the methodology used to achieve the research question and objectives of the thesis is presented.

CHAPTER 3: METHODOLOGY

This chapter presents the methodology used to achieve the research object. First, the setting of thesis project is presented follow by the justification of methodology choice. Lastly, we outline a brief overview of the methodology approach.

1. The setting of the thesis project

This thesis project is conducted as part of the **ReWork program** at SIRIC-ILIAD ("Site de Recherche Intégrée sur le Cancer", Imaging and Longitudinal Investigations to Ameliorate Decision-making). The overall objective of ReWork program is to provide new epidemiological findings about the social and occupational background of a patient during the initial cancer care and on the determinants of the QoL as well as the professional reintegration (RTW, retention of employment) after therapy. It is underpinned by the multidisciplinary expertise of the players in the Loire region in epidemiology, public health, psychology, occupational health, and ergonomics, having the coordination and use of health data from several cohorts (Constances and ELCCA) and the Loire Atlantique-Vendee cancer registry in common (SIRIC ILIAD, 2019). The program is organized into three axes (10, 11 and 12) and has led to the development of a theoretical-based clinical framework describing how to support breast or other cancer survivors at each stage of the RTW process (Porro et al., 2022a).

This thesis project is included in axe 12, which aims to develop simple tools intended for HCPs to help them identify patients who are at risk of having difficulties in returning to or retaining their employment, and to support them in the RTW process (SIRIC ILIAD, 2019).

2. Methodology approach

From the literature, we highlighted that the findings from studies that assessed the efficacy of PA on RTW in cancer survivors are contradictory. As a result, it is difficult to establish consistent evidence for the effectiveness of PA on RTW after cancer diagnosis. Therefore, we conduct this thesis project aims to evaluate the effects of PA on RTW after cancer diagnosis

and provide evidence of its effectiveness on RTW of cancer survivors. To answer the research question, we used an evidence synthesis methodology.

Evidence synthesis refers to the process and methods of bringing together evidence generated through primary research studies, whether qualitative, quantitative, or a combination of both, in order to answer research or decision-making questions (Langlois et al., 2018; Royal Society, 2018). According to Cochrane, evidence synthesis *"involves combining data from multiple studies investigating the same topic to comprehensively understand their findings and establish evidence for best practice*" (Cochrane, 2019). By integrating findings and data from many empirical studies, the evidence synthesis address research questions with a power that no single study has (Gough et al., 2020; Snyder, 2019). As such, it helps policy-makers, healthcare institutions, clinicians, researchers, and the public to make more informed decisions about health and healthcare (Cochrane, 2019).

In the field of health, evidence syntheses are used when there is a lack of appropriate evidence, the sample size of primary studies is too small to provide reliable and valid evidence, or there are contradictions in findings from primary studies available (Gough et al., 2020). There are many methods for conducting an evidence synthesis, depending on the purpose of the research and time constraints (Dixon-Woods et al., 2005; Grant and Booth, 2009; Pope et al., 2007). The methods are used to address a wide range of research questions, including the prevalence of different diseases, the evaluation of the effect of an intervention (i.e., medical or non-pharmacological therapy), the processes by which an intervention has an impact, and the meaning of different experiences for patients (Gough et al., 2019). In the case of this thesis, we use systematic review and meta-analysis, as well as rapid review methods to achieve our research questions. A brief overview of these methods is provided in the following.

2.1. Methods of the first study

To assess the effectiveness of PA interventions on RTW in cancer survivors (objective of study 1), we performed a systematic review and meta-analysis which are types of evidence synthesis methods. It is important to note that a systematic review and meta-analysis are

generally considered as methods that provide the best evidence for all clinical questions because they have the highest level of evidence (Ackley et al., 2007; Durieux et al., n.d.; Murad et al., 2016). As such, they are the gold standard in evidence-based research (**see Figure 6**). The key characteristics of these methods are:

- a clearly stated set of objectives with pre-defined eligibility criteria for studies, an explicit, reproducible methodology;
- a comprehensive search that attempts to identify and select all studies that would meet the eligibility criteria;
- an assessment of the validity of the findings of the included studies, for example through the assessment of the risk of bias; and
- a systematic presentation, and synthesis, of the characteristics and findings of the included studies (Higgins et al., 2019).

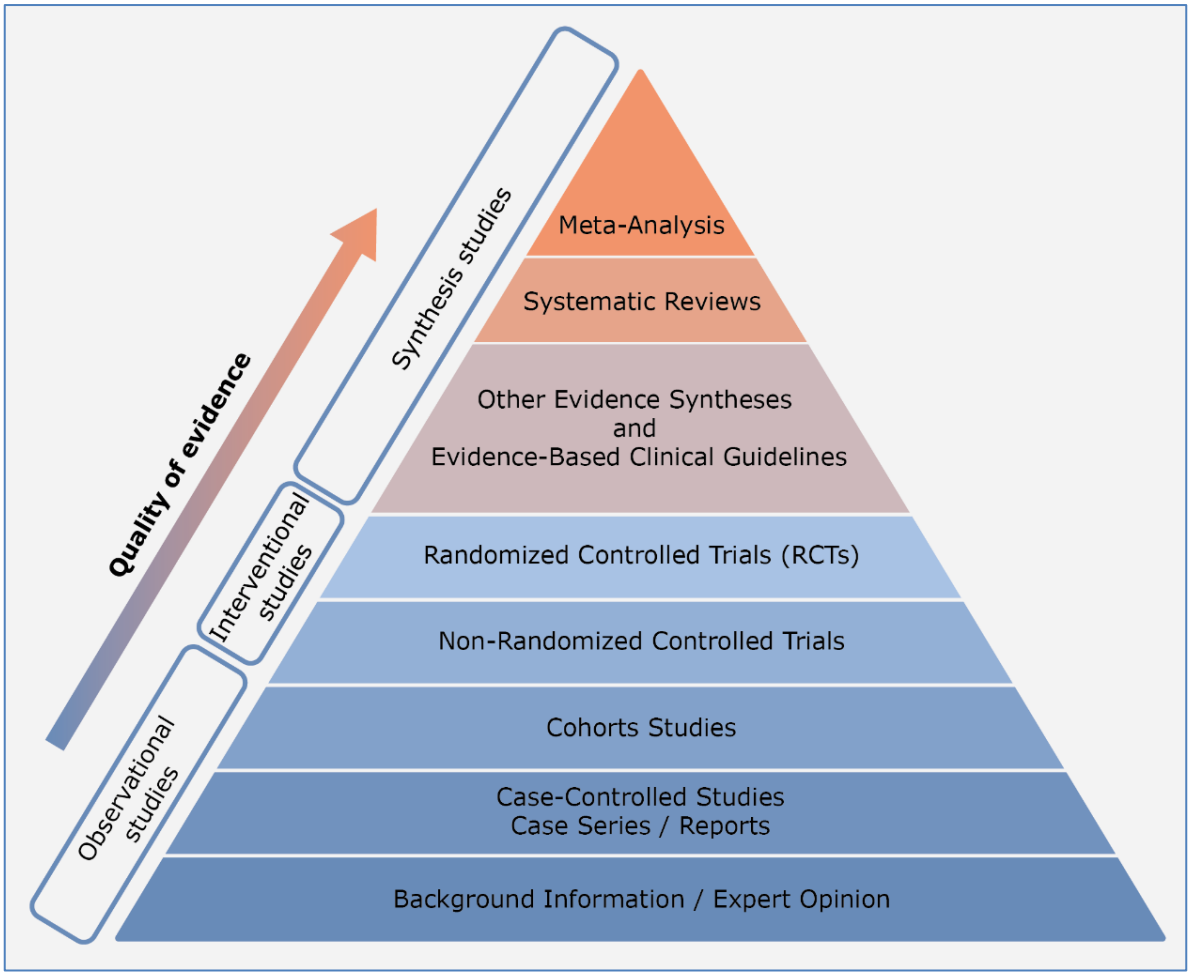

Figure 6. Types of studies and hierarchy of the quality of evidence (evidence pyramid).

Source: adapted from Tuffs University Evidence pyramid (Ellingson, 2023).

First, the systematic review is conducted following a rigorous scientific and reproducible process in several steps (Tawfik et al., 2019), as recommended by guidelines (Higgins et al., 2019; Page et al., 2021). The different steps followed to carry out the systematic review are presented in the **Figure 7**. In addition, we realized statistical analyses (meta-analysis) using data from the individual included studies to estimate the overall effect of PA on RTW (Deeks et al., 2019). Lastly, we performed a meta-regression to determine the appropriate dose of PA to improve RTW. Details of the study methods are described in the published article 1 (**see chapter 4**).

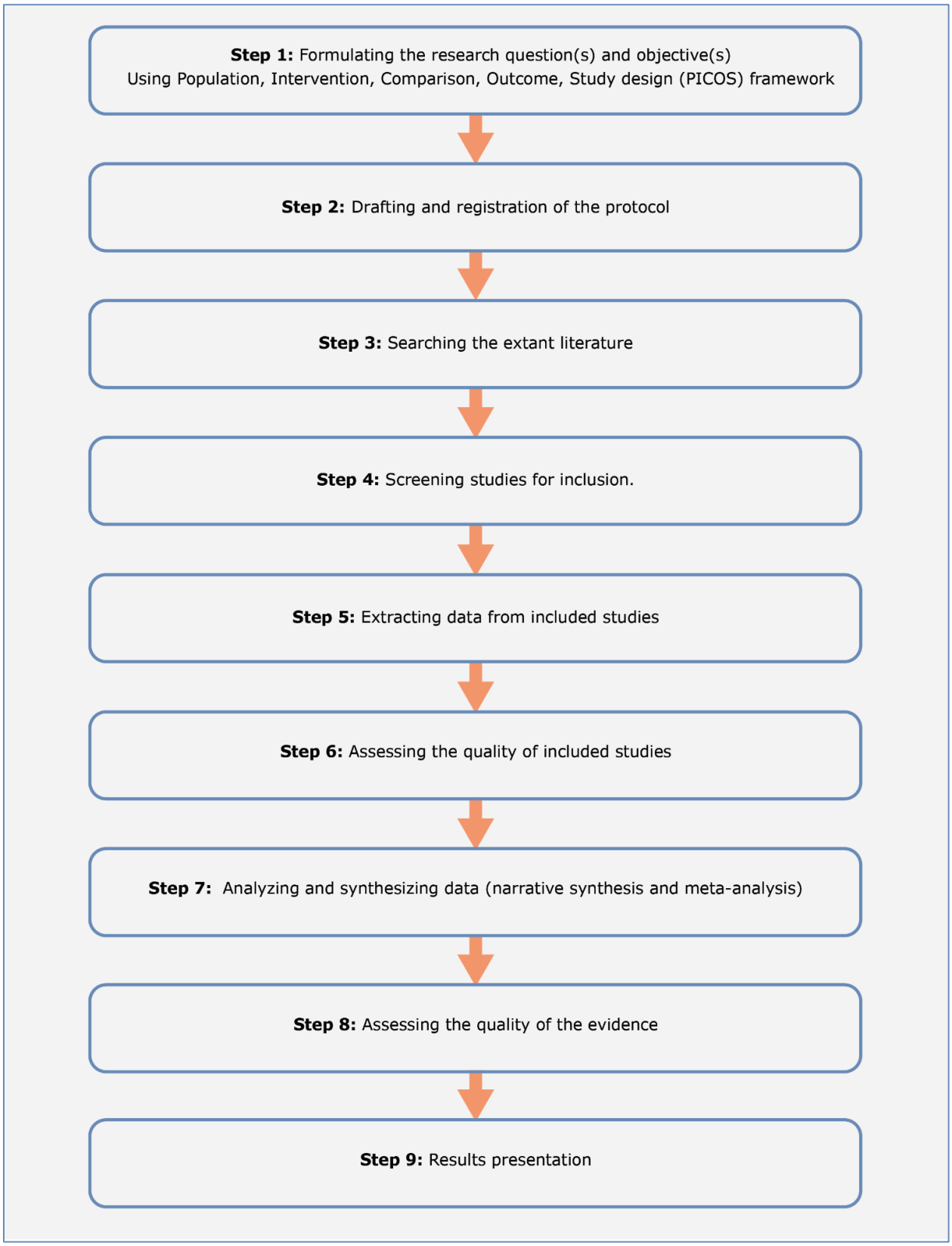

Figure 7. Steps for conducting systematic review and meta-analysis

2.2. Methods of study 2

To identify guidelines that recommend PA in people diagnosed with cancer and assess their quality (**objective of study 2**), we realize a rapid review in accordance to the Cochrane rapid review methods (Garritty et al., 2021). We searched scientific and grey literature databases, as well as websites of national and international organizations that provide recommendations in the field of oncology. Then, we assessed the methodological quality and transparency of the guideline development process using the 2nd version of Appraisal of Guidelines for Research and Evaluation tool (AGREE II checklist). Lastly, a descriptive analysis of the included guidelines has been performed followed by critical analysis of recommendations from guidelines judged to be of good quality. Details of the study methods are described in the published article 2 (**see chapter 4**).

2.3. Methods of study 3

Finally, to achieve the objective 3 of the thesis, we propose a guidance with practical protocols based on merged findings from previous studies (studies 1 and 2), combined with the expertise of a physical exercise professional experienced in cancer care. It is important to note that a clinical or care protocols are an agreed statement or rule about a specific clinical issue, with a precise sequence of activities to be adhered in order to manage a specific clinical condition (Hewitt-Taylor, 2004; National Clinical Effectiveness Committee, 2015). They provide a locally agreed standard to which clinicians and the organization can work. More specifically, the results from both studies were used to propose a first version of protocols, which was submitted for discussion to a physical exercise professional. A final version of protocols was proposed and validated during a second discussion. Details of the methods are described in article 3, in the process of submission (**see chapter 4**).

CHAPTER 4: RESULTS

In this chapter, we present the three studies conducted in this thesis and their results.

1. Study 1. Systematic review and meta-analysis for assessing the effectiveness of physical activity on RTW after cancer

This study aimed to assess the effectiveness of PA interventions on RTW in cancer survivors and determine the dose of PA needed to improve this outcome. It led to an article published on March 03, 2023, in **"Journal of Occupational rehabilitation"**. The findings from the study are summarized in key points below.

Key findings in four bullet points

- **Supervised PA** interventions including **aerobic and resistance exercises**, delivered during and/or after cancer therapy improved RTW in cancer survivors.
- The results revealed that PA interventions had a significant positive effect on RTW after cancer diagnosis compared to usual care.
- We found that an exercise dose between **7.6 METs-h/week and 15 METs-h/week** seems appropriate to improve RTW in cancer survivors. This corresponds to **100-120 minutes per week of moderate to vigorous exercise**, spread two times a week.
- Taken together, the findings of the first study provide with **moderate evidence that PA interventions are more effective than usual care in improving RTW** in cancer survivors.

To date, and to our knowledge, this is the first study that provide convincing evidence of the effectiveness of PA on RTW after cancer.

Journal of Occupational Rehabilitation (2023) 33:4–19
https://doi.org/10.1007/s10926-022-10052-9

REVIEW

Effectiveness of Physical Activity Interventions on Return to Work After a Cancer Diagnosis: A Systematic Review and Meta-analysis

Têtê Norbert Wilson[1] · Aboubakari Nambiema[1] · Bertrand Porro[1] · Alexis Descatha[1] · Agnès Aublet-Cuvelier[2] · Bradley Evanoff[3] · Yves Roquelaure[1]

Accepted: 2 June 2022 / Published online: 2 July 2022

Abstract

Purpose The aim of this study was to assess the effectiveness of physical activity (PA) interventions on return to work (RTW) in cancer survivors, compared to usual care, and to determine the dose of PA needed to improve this outcome. *Methods* A systematic review and meta-analysis were conducted according to PRISMA guidelines. Six electronic databases including PubMed, Embase, Web of Science, CENTRAL, PsycINFO, and Scopus were searched to identify studies, and completed by a search of grey literature and health organization websites. Two authors performed screening, selection, and data extraction independently. Study and intervention characteristics were extracted and summarized. Pooled risk ratio (RR) was estimated using a weight random-effects model with 95% confidence intervals (CIs). *Results* A total of 2655 records were identified, of which 8 intervention studies were included. The sample size of the included studies varied between 41 and 240, giving a total of 1087 participants aged between 18 and 75 years. Compared with usual care, PA interventions had a significant positive effect on RTW among cancer survivors with a pooled RR of 1.29 (95% CI 1.17, 1.42). We found that PA interventions (aerobic and resistance exercises) with an exercise dose between 7.6 METs.h/week and 15 METs.h/week, consisting in 50–60 min per session of moderate to vigorous physical exercise, twice a week seems relevant in improving RTW. *Conclusions* Our results showed, with moderate quality evidence that PA interventions are more effective than usual care in increasing the rate of RTW in cancer survivors.

Systematic Review Registration PROSPERO Registration Number, CRD42020203614.

Keywords Intervention · Return to work · Cancer · Physical activity · Systematic review

Background

Cancer is one of the leading causes of morbidity worldwide, with approximatively 19.3 million new cases diagnosed in 2020 [1]. Over the last few decades, advances in early detection and treatments have greatly contributed to the increased average survival of cancer patients.

Despite improved survival rates, it has been reported that cancer survivors usually experience long-term side effects from cancer and its treatment (e.g. cancer-related fatigue, pain, anxiety and depression) [2, 3]. These medical and psychological effects may become persistent, affecting the quality of life and work ability of cancer survivors (aged more than 18 years), and rendering it challenging to remain in or return to work (RTW) [4, 5]. Around 26 to 53% of cancer survivors will experience work loss and fail to RTW after diagnosis [6]. However, most of cancer survivors are motivated either to RTW or to be re-employed after treatment [7]. They regard returning to work as a symbol of full recovery and regaining a normal life [8]. Returning to work can also help maintain family income, improve self-esteem, sense of meaning, and health [8, 9].

Given the increasing number of cancer survivors at working age and the multiple challenges they face, there is a need to provide tailored programs supporting the RTW of cancer

✉ Têtê Norbert Wilson
tetenorbert.wilson@etud.univ-angers.fr

[1] Univ Angers, CHU Angers, Univ Rennes, Inserm, EHESP, Irset (Institut de Recherche en Santé, environnement et travail) - UMR_S 1085, 49000 Angers, France

[2] Direction des Etudes et de Recherches, INRS (Institut National de Recherche Et de Sécurité), 1 rue du Morvan, CS60027, 54519 Vandœuvre-lès-Nancy, France

[3] Division of General Medical Sciences, Washington University School of Medicine, St. Louis, MO 63310, USA

survivors [10]. Physical activity (PA) has been shown as an effective intervention to address some of the side effects from treatment [11], by decreasing fatigue and/or emotional distress levels and increasing the level of perceived quality of life of patients affected by cancer [12]. Based on these findings, several interventions including PA have been developed to help cancer survivors to RTW after cancer diagnosis [13–15]. Some systematic reviews of rehabilitation interventions revealed that PA could contribute to improving RTW rates [13–16], while another review showed that PA interventions were not more effective than care as usual [17]. These contradictory results could be explained by the fact that previous systematic reviews included several interventions namely psychosocial, vocational, educational and multidisciplinary interventions and did not investigate the specific effect of PA on RTW in cancer survivors [13–16]. Moreover, the conditions for implementing PA interventions in terms of content and delivery (e.g., period, setting and mode of delivery) remains little explored in these systematic reviews [13–15].

Finally, the exercise dose–response and the best type of exercise in terms of duration, frequency and intensity of PA required to improve RTW remain unclear, making it difficult to recommend a specific exercise protocol for cancer survivors in the RTW intervention programs [18].

To the best of our knowledge, no systematic review to date, has specifically evaluated the effectiveness and dose–response of PA interventions on RTW in cancer survivors. Therefore, we conducted this systematic review to assess the effectiveness of PA intervention on RTW in cancer survivors compared to usual care, and to determine the dose of PA needed to improve this outcome. Based on the results achieved, recommendations will be suggested for implementation of PA interventions to support RTW in cancer survivors.

Methods

This review was conducted following the Preferred Reporting Items for Systematic review and Meta-Analysis (PRISMA) guidelines [19]. The review protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) under number CRD42020203614.

Eligibility Criteria

Studies were included in this systematic review if they met the following PICOS criteria (Population, Intervention, Comparator, Outcomes and Study design): (i) randomized controlled trials (RCTs) or non-randomized controlled trials (nRCTs), (ii) conducted on participants (working adults, aged ≥ 18 years old) diagnosed with cancer (all location) and who were in paid employment (employee or self-employed) at the time of diagnosis, (iii) including any type of PA as interventions, carried out in any setting (clinical setting, or at home), prior, during or after treatment, supervised or unsupervised, (iv) compared to usual care, and (v) assessed RTW as outcome (rates of RTW or time to RTW). The control group participants included patients receiving usual or standard care and who did not follow or participate in the PA intervention. We included studies without restriction on publication dates.

Studies were excluded if they: concerned retired cancer survivors or pediatric cancers (childhood and young adults' cancers); did not have a control group; did not assess RTW as an outcome; and/ or were not meet the design of intervention studies (case reports, case series, editorial, reviews, cross-sectional, case control and cohort studies).

Information Sources and Search Strategy

To identify records, the following electronic databases were consulted: PubMed, Embase, the Cochrane Library, Web of Science, PsycINFO, and Scopus. Unpublished and ongoing studies were identified by searching a clinical trial database (Clinical Trial Gov), a grey literature database (OpenGrey), health organization websites and internet search-engine databases, such as: European Agency for Safety and Health at Work (OSHA), American Society of Clinical Oncology (ASCO), the French National Cancer Institute (INCA) and Google Scholar. In Google Scholar, only the first 200 hits were selected after ordering the hits by relevance. In addition, the reference lists of included studies and previous systematic reviews were hand searched in order to identify additional relevant studies. Finally, two experts were contacted (by e-mail) based on their scientific expertise, and publications on the topic, to provide information of known published or unpublished studies that should be included in this review.

The search strategy was based on PubMed and adapted to the specificity of each database. Keywords related to cancer, PA and RTW were identified and selected from Mesh database and earlier systematic reviews [16, 17]. The relevant keywords in Medical Subject Heading "[Mesh]" and text word "[TW]" terms were connected with Boolean operators "AND"/" OR" to build the search query. Some search terms were truncated to include variations in word endings, spellings, and database indices. In Google Scholar, OSHA and ASCO databases, filters were applied to refine the search output. The search strategy was modified to fit the specifics of other databases. Two external librarians reviewed the research query to make it more relevant. All searches were conducted using English language terms.

Records were searched in all databases from inception to December 8, 2020 and updated on September 30, 2021.

Detailed search strategies for each database are available in Supplementary Table A.

Study Selection

Study selection was carried out using the Covidence systematic review software [20]. All study records identified in the search were downloaded and duplicates were removed. After removing the duplicates, studies were screened for inclusion/exclusion decisions in two stages. Two review authors (TNW and AN), independently screened titles and abstracts (*step 1*), and then full texts (*step 2*) of potentially relevant records. Discrepancies between authors were resolved through discussion to reach consensus.

Data Extraction

A standard data extraction form was developed and trialed until data extractors reached convergence and agreement. Two review authors (TNW and AN) independently extracted data from included studies. The following data were extracted from each included study feature (author, year of publication, country, and study design); population characteristics (sample size, age, sex, and type of cancer), interventions characteristics (type of PA, frequency, duration, intensity, exercise dose, intervention length, area, period, and mode of delivery). Data regarding control group (e.g., standard care, or usual care), outcomes; and main findings were also extracted. All discordances between data extractors were resolved by discussion to reach consensus.

Exercise Dose Calculation

Exercise dose was estimated using metabolic equivalent for task (MET), where 1 MET equates to 3.5 mlO_2/kg/min. The corresponding MET values for exercise intensity were coded according to the compendium of PA [21] if no more details related to their content were provided and study's authors did not respond to requests for the missing data. Thus, 3.8 and 6 METs were respectively assigned to moderate and vigorous intensity of resistance exercise; strength-training exercise was coded 3.5 METs; warm-up and cool-down were estimated at 2.5 METs. Yoga and stretching activities were coded to 2.8 METs. For interventions comprising several types of exercises of different duration, the average duration of each exercise was computed to estimate exercise dose. The estimation of a targeted exercise dose was calculated as:

$$\text{Weekly exercise dose} = \sum_{i=1}^{n} (Intensity)_i \times (Duration)_i \times (Frequency)_i \text{inMET.h/week},$$

where one exercise session is composed of i PA, the intensity of PA i is in METs, the average duration of PA i is in hours, and frequency is the number of sessions per week.

Dealing with Missing Data

During data extraction, if there are missing data in studies, the study's authors were contacted by e-mail using the contact details provided in the article to obtain data that were missing in their report, which we needed as input. Follow-up e-mails were sent two weeks later if responses were not received. If responses were still not received after the reminder, and to be exhaustive in our research, the studies were retained in the systematic review and used for the narrative synthesis.

Risk of Bias Assessment in Individual Studies

The Navigation Guide risk of bias tool was used to assess the risk of bias across included studies [22]. It was developed according to the standard risk of bias assessment methods of the Cochrane Collaboration [23], the Agency for Healthcare Research and Quality (AHRQ) [24] and adapted specifically to systematic review in occupational health. The tool has been successfully applied in several systematic reviews [25–29] and used by the World Health Organization (WHO) and International Labor Organization (ILO) experts network [30, 31]. Nine domains of bias were included in the Navigation Guide for human studies. For each domain, the risk of bias rating was "low risk"; "probably low risk"; "probably high risk"; "high risk"; or "not applicable". The risk of bias assessment was conducted on the individual study level and across the body of evidence for each study. Two review authors (TNW and AN) independently assessed the risk of bias for each study by outcome. When the authors' individual assessment differed, disagreements were resolved by discussion to reach consensus.

Outcomes Measures and Intervention Effect

The outcome considered in our study was RTW after cancer diagnosis (including prior, during or after treatment). The RTW included any return to full-time, or part-time employment, to previous or new employment, and to either the same or reduced role after a sick leave due to cancer [17]. It was measured as rate of RTW (binary outcome) or time to RTW (continuous outcome). The rate of RTW is defined as the

proportion of patients who returned to work in each arm (intervention and control) at the endpoint, whilst the time to RTW is the number of days between reporting sick leave and any work resumption or the number of days on sick leave during the follow-up period. The risk ratios (RRs) were used as the measure of intervention effect (effect size). They were calculated from the reported values of outcomes. All estimates were reported with their 95% confidence interval (CI) or P value.

Assessment of Heterogeneity

First, we decided whether or not studies were sufficiently homogeneous to be able to synthesize the results into meta-analysis (pooled effect size). Studies were sufficiently homogeneous when they had similar designs, similar intervention and comparator, and similar outcome measure. Statistical heterogeneity was also tested with I^2 statistic [32]. Studies were statistically heterogenous if I^2 was greater than 50%.

Synthesis of Results (Data Synthesis)

First, a narrative synthesis of the results from included studies was performed following the Popay et al. [33] framework for narrative synthesis. Secondly, meta-analysis was conducted to estimate the overall effect of PA on RTW by pooling the RRs of each study according to the Mantel–Haenszel method. A random effects model was used to estimate the overall effect size.

Sensitivity Analyses

Two sensitivity analyzes were conducted excluding one arm of intervention for the 3-arms RCTs. A meta-regression was also performed from included studies that presented complete data on PA characteristics to assess the association between exercise dose and intervention effects (RRs). Statistical analyzes were performed using RevMan version 5.4 and R 4.1.1 software. Statistical significance was set at alpha 5% (P value < 0.05) for all results.

Publication Bias

According to Cochrane Collaboration, tests for funnel plot asymmetry should be used to judge concerns on publication bias when there are at least 10 studies included in the meta-analysis [34, 35]. If there are fewer than 10 studies, the power of the tests is too low to distinguish chance from real asymmetry [35]. In this case, the risk of publication bias was judged qualitatively.

Quality of Evidence Assessment

The quality of evidence for the entire body of evidence was assessed using the Navigation Guide approach for grading the quality and strength across human studies [27]. The Navigation Guide is based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach [36] and adapted specifically to systematic review in occupational health. However, the Navigation Guide allows for rating evidence based on the following 8 domains: (i) risk of bias; (ii) inconsistency; (iii) indirectness of evidence; (iv) imprecision of the pooled estimate; and (v) possibility of publication bias; (vi) large magnitude of effect; (vii) dose–response; and (viii) residual confounding [37]. Two review authors (TNW and AN) independently assessed the quality of evidence for the entire body of evidence, and any disagreements were resolved by consensus. The entire body of evidence was graded using the three Navigation Guide standard quality of evidence ratings: "high", "moderate" and "low" [25].

Results

Search Results and Study Selection

Figure 1 presents the PRISMA flow diagram of the studies selection process. A total of 2655 records were identified including 1983 from database searches and 672 through other sources. Of these, 758 were duplicates and removed, leaving 1897 records for screening. The screening of titles and abstracts excluded 1871 studies that did not meet the eligibility criteria and included 26 articles for full-text stage. Following review of full-text articles, 18 studies were excluded and only 8 fulfilled all eligibility criteria for inclusion [38–45]. The reasons for exclusion of the 18 studies were: study with wrong design (n = 9), without control group (n = 6), without RTW outcomes (n = 2), and without PA intervention (n = 1).

Description of Included Studies

In this section, the characteristics of studies, participants, and interventions, as well as comparators and outcomes are described and presented in Table 1.

Characteristics of Studies

Of the 8 included studies, 5 were published after 2010 [40–44], while the remaining 3 studies were published before (1994, 2006, and 2009) [38, 39, 45]. Seven studies were RCT [38–42, 44, 45], one was nRCT [43]. All included studies were conducted in high income countries, with most

carried out in European countries (n = 5), particularly in the Netherlands [41, 41, 43, 44] and Sweden [38, 42]. The other 3 studies were conducted in North American countries: USA [38, 39] and Canada [40].

Characteristics of Participants

The sample size of included studies varied between 41 and 240 at inclusion, for a total of 1087 participants aged between 18 and 75 years. Most studies (n = 5) included women exclusively [38, 40–42, 45], one study included men exclusively [39], and the samples were mixed sex in 2 studies [43, 44]. More than half of the included studies (n = 5) involved breast cancer survivors exclusively [40–42, 44, 45]. Of these 5 studies, 3 specifically reported information of the tumor stage (from I to III). One study included prostate cancer survivors [39]. The remaining studies (n = 2) included participants with mixed cancer diagnoses: breast cancer (mainly), colorectal, upper gastrointestinal, Hodgkin lymphoma, ovarian, and other cancers [38, 43].

Intervention characteristics

Details on the interventions are presented in Table 1. Six studies included one intervention group [38–41, 43, 45], while 2 studies were 3-arm RCTs comparing 2 intervention groups to usual care [42, 44], leading to the inclusion of 10 intervention groups, each one compared with usual care.

The implementation of interventions varied widely. Of the 10 interventions, 5 were delivered in a hospital setting [38, 42–44], one was a home-based intervention [44], and 4 combined hospital and home-based sessions [39–41, 45]. The intervention length ranged from 7 to 24 weeks, and the majority (n = 8) were supervised. The mode of intervention delivery was reported as supervised when the PA was performed under the direct supervision of an instructor (by qualified or trained personnel including nurses, physical therapists, or physiotherapists) and non-supervised otherwise. Four periods were reported for the time that interventions were administered: (i) intervention delivered before treatment [39], (ii) intervention initiated 1–2 weeks before the therapy and finished during treatment [41], (iii) intervention began during treatment and finished a few weeks after treatment [42, 44], and (iv) intervention administered after the completion of treatment [38, 40, 43, 45]. The period before treatment includes the time from cancer diagnosis until the beginning of treatment.

The majority of PA interventions were reported with the FITT (Frequency, Intensity, Time, and Type of exercise) components of exercise. All studies reported the type of PA including resistance exercise, aerobic exercise, endurance exercise, strength training, and Yoga (see details in Supplementary Table B). Most of the interventions (n = 7) involved PA only [40–44]. Of these, 2 interventions included aerobic exercise [42, 44], one included resistance exercise [42], 2 included a combination of resistance and aerobic exercises [43, 44], and 2 included multicomponent exercises [40, 41]. In the remaining studies (n = 3), exercise was combined with other interventions [38, 39, 45].

The frequency, duration and intensity of exercise varied across studies. All studies reported the frequency, which varied from 1 to 5 sessions per week. The exercise session duration was reported for 6 intervention groups and each exercise session lasted between 30 to 75 min [41, 42, 44, 45]. The duration of each session was constant in 4 intervention groups, whereas in 2 interventions [41, 44] it was estimated from the duration of different types of exercises that comprised the intervention. The exercise intensity was reported for 7 intervention groups [41–45]. It varied from 2.8 MET (low intensity) to 9 MET (high intensity) for each session. For all studies, PA intervention was performed according to standardized protocol followed by each participant.

Control Group (Comparator)

All studies compared the intervention to usual care as the control group. The number of participants in control groups varied from 19 to 89. The usual care was not described in the majority of included studies. Only the studies of Rogers et al. [45] described the usual care group. In this study, the usual care group was provided written materials related to physical activity obtained from the American Cancer Society. These materials were considered as usual care because of their availability to the general public. No specific instructions were given to the usual care group concerning PA behavior change [45].

Outcomes

All studies were interested in RTW as primary (n = 2) or secondary (n = 6) outcomes at different follow-up durations (endpoint). RTW was measured as event rates (binary outcome) such as rate of RTW rates in 7 studies [38–44]. One study reported Log odds as the outcome measure [45]. Outcomes were assessed at various endpoints that varied from 6 to 18 months after baseline (post-intervention). All the included studies did not report details on the meaning of RTW. Only three studies provided information about RTW as a return to full-time or part-time employment [42–44].

Risk of Bias in Included Studies

The risk of bias assessment for each included study and by domain is summarized in Fig. 2. All studies were deemed *probably low risk* for detection biases (intervention and

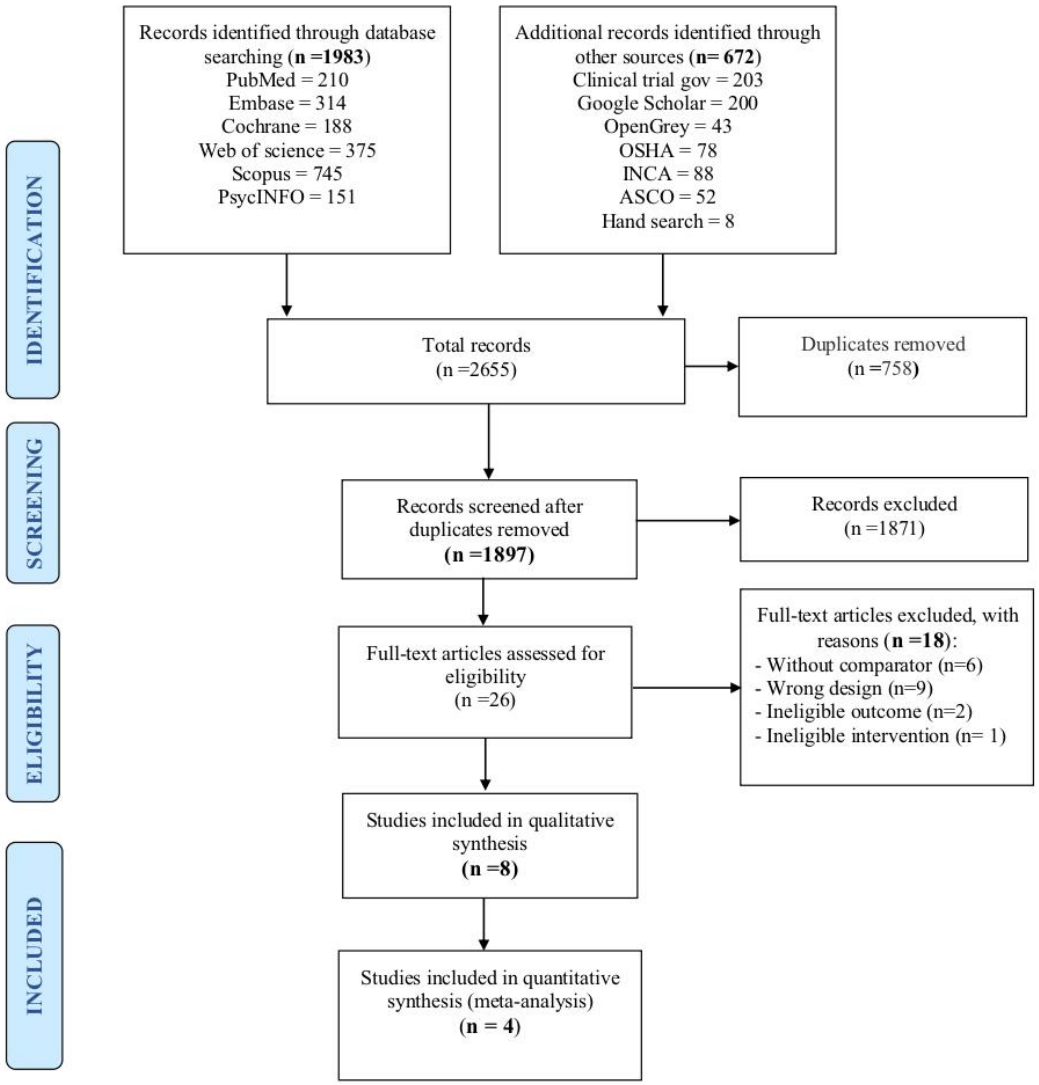

Fig. 1 Flow diagram of study selection

outcome assessment), reporting bias and confounding. This is due to the fact that PA interventions were performed by each participant following a standardized protocol and the outcomes were assessed using a standard metrics tool for all patients. Furthermore, for the risk of confounding, we considered that the randomization minimizes confounders, and this is not expected to introduce substantial bias. For the remaining domains of bias (selection bias, performance bias, attrition bias, conflict of interest, and other risk of bias), at least one of the studies was judged as being at *high risk of bias*.

For further details, the justification for each rating for each domain, by study is presented in Supplementary Table C.

Synthesis of Results

Meta-analysis was limited to the studies that exclusively compared PA intervention to usual care. A narrative synthesis was also performed according to the results of individual studies (see Table 1).

Table 1 Characteristics of included studies in the systematic review

Study characteristics				Study population			
Study ID	Country of study	Study period (day/month/year)	Study design	Number of participants included	Age, range (years)	Sex (n)	Type of cancer (n)
Mijwel et al. [42]	Sweden	03/2013–07/2016	RCT	240	18–70	Women (240)	Breast (240)
Jong et al. [41]	Netherlands	NR	RCT	83	18–70	Women (83)	Breast stage I–III (83)
Ibrahim et al. [40]	Canada	2011–2015	RCT	59	18–45	Women (59)	Breast stage I–III (59)
Van Waart et al. [44]	Netherlands	03/2010–12/2012	RCT	230	51	Women (228) Men (2)	Breast (230)
Thijs et al. [43]	Netherlands	07/2001–06/2005	nRCT	110	18–65	Women (93) Men (17)	Breast (77) Colorectal (10) Hodgkin lymphoma (10) Others (13)
Burgio et al. [39]	USA	01/1996–01/2001	RCT	125	53–68	Men (125)	Prostate (125)
Rogers et al. [45]	USA	04/2006–04/2007	RCT	41	18–70	Women (41)	Breast stage I–IIIa (41)
Berglund et al. [38]	Sweden	NR	RCT	199	< 75	Women (199)	Breast (159) Ovarian (16) Others (24)

Characteristics of interventions										
Study ID	Type	Length[a] (week)	Fre-quency (session/week)	Duration[b] (min/session)	Intensity (MET)	Exercise dose[c] (MET.h/week)	Area of delivery	Period of delivery	Delivery modes	Number of participants with outcome
Mijwel et al. [42]	RT-HIIT: resistance exercise followed by high-intensity interval training	16	2	60	3.80	7.60	Hospital	During and after treatment	Supervised	59
	AT-HIIT: aerobic exercise followed by high-Intensity interval training	16	2	60	6.00	12.00	Hospital	During and after treatment	Supervised	62
Jong et al. [41]	Dru yoga (breathing awareness, Energy block release; body awareness, relaxation)	12	1	75	2.80	3.55	Home and hospital	Before and during treatment	Supervised	40
Ibrahim et al. [40]	Exercise program: Cardiovascular exercise, strength training, endurance program and stretching program	12	3	NR	NR	NA	Home and hospital	After treatment	Supervised	29
Van Waart et al. [44]	Onco-Move: aerobic exercise	20	5	30	4.00	10.00	Home	During and after treatment	Not supervised	62
	OnTrack: resistance and aerobic exercise	20	2	50	9.00	15.00	Hospital	During and after treatment	Supervised	71
Thijs et al. [43]	Resistance and aerobic exercise	18	2	NR	6.00	NA	Hospital	After treatment	Supervised	72
Burgio et al. [39]	Strength exercise + Biofeedback assisted behavioral training	24	3	NR	NR	NA	Home and hospital	Before treatment	Not supervised	28
Rogers et al. [45]	Aerobic exercise + group discussions + counseling	12	3	50	3.80	9.50	Home and hospital	After treatment	Supervised	20
Berglund et al. [38]	Strength exercise + coping skills + information	7	2	NR	NR	NA	Hospital	After treatment	Supervised	87

Table 1 (continued)

Study ID	Comparator		Outcome assessment			Studies' conclusion (main results)
	Type	Number of participants with outcome	Definition and endpoint	Type	Effect measure	
Mijwel et al. [42]	Usual care	52	RTW at 12 months (part time)	Secondary	Rate of RTW: 82.00% for RT-HIIT 91.00% for AT-HIIT 69.00% for usual care, P value = 0.020	At 12 months, both RT-HIIT and AT-HIIT displayed beneficial effect on RTW. The difference remained significant for AT-HIIT
Jong et al. [41]	Usual care	27	RTW at 6 months	Secondary	Rate of RTW: 53.00% for Yoga 23.00% for usual care	Possible favorable effects of the yoga program on early return to work in breast cancer survivors
Ibrahim et al. [40]	Usual care	30	RTW at 18 months	Secondary	Rate of RTW: 86.00%	The majority of participants returned to work
Van Waart et al. [44]	Usual care	64	RTW at 6 months (part time or full time)	Secondary	Rate of RTW: 83.00% for Onco-Track 79.00% for Onco-Move 61.00% for usual care, P value = 0.012	At 6 months, both intervention groups had significantly higher RTW rates than usual care (returned earlier to work than the control group). The Onco-track program was most effective in facilitating return to work
Thijs et al. [43]	Usual Care	38	RTW at 12 months and time to RTW (full time)	Primary	Rate of RTW: 78.00% for intervention group 66.00% for control group P value = 0.180	An oncologic rehabilitation program including high-intensity physical training results in substantial benefits effect by improving job resumption. No significance was found in RTW rate between groups
Burgio et al. [39]	Usual care	29	RTW at 6 months	Secondary	Rate of RTW: 78.60% for intervention group 79.30% for control group, P value: 0.950	The finding was not accompanied by differences in the proportion of men who returned to work or usual activities by the 6-month follow-up. No difference was found on RTW
Rogers et al. [45]	Usual care[d]	19	Time to RTW (number of sick days in past month)	Secondary	Log odds: For Intervention group = 0.20 For usual care = − 0.20, P value = 0.800 OR = 1.49	The intervention did not significantly change in number of sick days missed from work
Berglund et al. [38]	Usual care	89	RTW (work status) at 12 months	Primary	Rate of RTW: 74.60% for intervention group 60.90% for control group	No significant difference between intervention and control groups in the rate of RTW

n number of participants, *RCT* randomized controlled trials, *nRCT* non-randomized controlled trials, *USA* United States of America, *MET* Metabolic Equivalent of Task (Low: <3MET, moderate: 3–6 MET and high: ≥ 6 MET), *RT-HIIT* Resistance Training combined with High-Intensity Interval Training, *AT-HIIT* Aerobic Training combined High-Intensity Interval Training, *RTW* return to work, *OR* odds ratio, *NA* not applicable, *NR* not reported

[a]Length of intervention, [b]mean duration of exercise sessions, [c]exercise dose = (Intensity) × (duration) × (frequency), [d]Usual care: the usual care group was provided written materials related to physical activity obtained from the American Cancer. These materials were considered "usual care" because of their availability to the general public

Effects of PA Interventions on RTW at 12 Months: Meta-analysis

Figure 3 presents the results of meta-analysis. Due to data availability, a meta-analysis was possible only for the 4 studies that reported the rate of RTW for both the PA intervention group and control group [41–44]. Of these, 2 studies were 3-arm intervention trials [42, 44] leading to the inclusion of 6 studies in meta-analysis. Pooled estimates using random effects model showed that there is no heterogeneity among studies ($P=0.55$, $I^2=0\%$). The results of meta-analysis showed a significant effect of PA interventions on RTW compared to usual care with a pooled overall RR of 1.29 (95% CI 1.17, 1.42). These results mean that PA intervention is more effective than usual care in improving RTW in cancer survivors.

Sensitivity Analyses

Two sensitivity analyzes were performed excluding one-arm of intervention for the 3-arm RCTs. First, the intervention groups, AT-HIIT and OnTrack were excluded in the meta-analysis (see Fig. 4), and then RT-HIIT and Onco-Move groups were excluded (see Fig. 5). The results always showed the lack heterogeneity among the studies with $I^2=15\%$ and $I^2=6\%$ respectively. They also showed a statistically significant effect on RTW in favor of PA interventions compared to usual care. The pooled RR were respectively 1.25 (95% CI 1.07, 1.45) and 1.32 (95% CI 1.16, 1.51).

Effects of Interventions on RTW: Narrative Synthesis

The main results from individual studies were reported in Table 1. Of the 8 included studies, 2 studies reported a statistically significant effect of PA interventions for increasing the rate of RTW [42, 44]. Findings from Mijwel et al. [42] indicated that participating in supervised aerobic exercise (in both groups: AT-HIIT and RT-HIIT) significantly increased rates of RTW (91% and 82% respectively) than usual care (69%). Similarly, results from the Van Waart et al. [44] study showed a significant increased rate of RTW for both intervention groups (OnTrack and OncoMove programs) with RTW rates of 83% and 79% compared to 61% for usual care, respectively. Authors concluded that a supervised combined aerobic and resistance exercise (OnTrack program) was the most effective in improving RTW. Likewise, 2 studies reported positive effects in favor of PA with an increased rate of RTW compared to usual care [41, 43]. The Jong et al. study [41] reported that 53% of patients were RTW at 6 months in the intervention group compared to 23% in the control group. In addition, Thijs et al. [43] found that 78% of patients in the intervention group were returned to work at 12 months compared to 68% of usual care. The Ibrahim et al. [40] study did not report the RTW rate in the control group. However, the authors concluded that the majority of participants (86%) in the intervention group returned to work.

The remaining 3 studies were multidisciplinary intervention studies that combined PA with other interventions [38, 39, 45]. Findings from these studies indicated positive effects of interventions on RTW compared to usual care. In the study by Berglund et al. [38] the rate of RTW was higher for participants in the intervention group (74.6%) compared to usual care (60.9%). Rogers et al. [45] observed an effect size of 1.49 for sick days in favor of the intervention group.

Overall, findings from included studies indicated that PA interventions improve RTW for cancer survivors compared to usual care.

Effects of Exercise Dose

The exercise dose was estimated from 4 studies that provided complete data for 6 interventions groups [41, 42, 44, 45] (see Table 1). The weekly exercise dose ranged from 3.55 to 15 MET.h/week. A statistically significant effect was observed on RTW for the exercise dose in 2 studies [42, 44]. The study of Mijwel et al. [42] used 2-arm intervention groups (resistance exercise and aerobic exercise) compared to usual care. The exercise dose was estimated at 7.6 METs.h/week for resistance exercise (RT-HIIT group) and 12 METs.h/week for aerobic exercise (AT-HIIT group), corresponding respectively to 60 min per session of moderate and high intensity PA twice a week. The study by Van Waart et al. [44] also included 2-arm intervention groups consisting of 30 min per session of moderate-intensity aerobic exercise 5 times per week (Onco-Move group), and 50 min per session of high-intensity combined aerobic and resistance exercise, twice a week (OnTrack group). This equated to a weekly exercise dose of 10 METs.h/wk and 15 METs.h/wk, respectively. The authors concluded that moderate to high intensity combined resistance and aerobic exercise (i.e., 15 METs.h/week) is most effective in facilitating RTW for cancer survivors.

The meta-regression exploring the relationship between weekly dose of exercise and RR revealed a positive linear relation for RTW (regression coefficient = 0.024; $P=0.0703$) (see Fig. 6). According to these results, we can suggest that effect of PA on RTW would be observed with a weekly dose of aerobic and resistance exercise between 7.6 METs.h/week and 15 METs.h/week (i.e., at least 50 to 60 min per session of moderate to high intensity PA twice a week).

Quality of Evidence Assessment

The latest Navigation Guide instructions used by Descatha et al. [30] was adopted for grading the quality of evidence.

	1. Mijwel et al. (2019)	2. Jong et al. (2018)	3. Ibrahim et al. (2017)	4. Van Waart et al. (2015)	5. Thijs et al. (2012)	6. Burgio et al. (2006)	7. Rogers et al. (2009)	8. Berglund et al. (1994)
1- Selection bias	LOW	PROBABLY LOW	LOW	PROBABLY LOW	PROBABLY HIGH	LOW	LOW	PROBABLY LOW
2- Performance bias (blinding)	PROBABLY LOW	PROBABLY LOW	PROBABLY LOW	PROBABLY LOW	PROBABLY HIGH	PROBABLY LOW	PROBABLY LOW	PROBABLY LOW
3- Detection bias (intervention assessment)	PROBABLY LOW	PROBABLY LOW	PROBABLY LOW	PORBABLY LOW	PROBABLY LOW	PROBABLY LOW	PROBABLY LOW	PROBABLY LOW
4- Detection bias (outcomes assessment)	PROBABLY LOW	PROBABLY LOW	PROBABLY LOW	PROPABLY LOW	PROBABLY LOW	PROBABLY LOW	PROBABLY LOW	PROBABLY LOW
5- Confounding	PROBABLY LOW	PROBABLY LOW	PROBABLY LOW	PROPABLY LOW	PROBABLY LOW	PROBABLY LOW	PROBABLY LOW	PROBABLY LOW
6- Attrition bias (incomplete outcome data)	PROBABLY HIGH	PROBABLY HIGH	PROBABLY HIGH	PROBABLY LOW	PROBABLY LOW	PROBABLY LOW	PROBABLY LOW	PROBABLY LOW
7-Reporting bias	PROBABLY LOW	PROBABLY LOW	PROBABLY LOW	PROBABLY LOW	PROBABLY LOW	PROBABLY LOW	PROBABLY LOW	PROBABLY LOW
8- Conflict of interest	LOW	LOW	LOW	PROBABLY LOW	LOW	LOW	LOW	LOW
9- Other risk of bias	PROBABLY HIGH	PROBABLY LOW	PROBABLY HIGH	PROBABLY LOW	PROBABLY HIGH	PROBABLY HIGH	LOW	PROBABLY HIGH

Fig. 2 Summary of risk of bias assessment

The risk of publication bias was assessed qualitatively because the number of included studies is lower than ten.

We did not have any serious concerns regarding inconsistency, because of the lack of heterogeneity ($I^2 = 0\%$, $P < 0.05$) and the estimated RRs varied little across the studies. There were also no serious concerns regarding risk of publication bias because none of the included studies were sponsored by the industry, and we used comprehensive searches of the literature including grey literature. For indirectness, we did not have serious concerns, regarding the combination of the outcome definition, including "mixed" (rate of RTW and time to RTW), and because population, intervention and outcome did not differ from those of interest. We also had no concerns regarding imprecision given the narrow CIs in the pooled effect size estimates. Therefore, the quality of evidence was not downgraded for inconsistency, imprecision, indirectness, and risk of publication.

bias. There were very serious concerns regarding risk of bias in the body of evidence because the risk of bias was judged to be probably high, and we therefore downgraded by two levels (− 2). We did not upgrade for a large effect estimate, or for evidence for a dose–response and residual confounding. In conclusion, we started at "high" for randomized studies and downgraded by two levels (− 2) for risk of bias to a final rating of "moderate".

Discussion

Main Findings

The aim of this systematic review was to assess the effects of PA intervention on RTW in cancer survivors and determine the dose of PA needed to improve this outcome. Only 8 relevant studies were included in this review, because of the paucity of PA interventions to support RTW in cancer survivors. The sample size of included studies varied from 41 to 240 for a total of 1087 participants aged between 18 and 75 years. The small sample size of the included studies may be due to the difficulties and barriers of cancer survivors to be enrolled in clinical trials [46, 47]. We included studies with participants aged up to 75 years. This is explained by the fact that the retirement age in some countries is up to 67 years [48]. Moreover, in our eligibility criteria we have taken into account the self-employed who did not have a limit for working age.

Through meta-analysis, we found a significant effect in favor of PA intervention on RTW compared to usual care. The results from narrative synthesis also revealed positive effects in favor of PA with an increased rate of RTW compared to usual care. These results could be interpreted by the moderate mediation effects of PA through the conceptual models of RTW after cancer diagnosis [10, 49–51], and by the biological effects of PA [52]. Physical activity might deal with RTW through its mediation effects on immune processes, possibly related to chronic inflammation, and its impact on psychosocial outcomes (quality of life and fatigue). Exercise intervention studies have reported results on the reduction of inflammatory biomarkers associated with cancer including C-reactive protein (CRP), interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α). Physical activity, especially resistance training, decreased leptin levels, TNF-α and insulin secretion, and increased adiponectin secretion over a seventy-two hour period, which helps to reduce chronic inflammation induced by intra-abdominal fat [53, 54]. According to conceptual models, several determinants including sociodemographic factors, disease-related factors, treatment-related factors, work-related factors, and psychosocial factors (e.g., quality of life, fatigue, and others) interact to impact the RTW of cancer survivors. There is consistent evidence that PA improves quality of life and fatigue in cancer survivors, regardless of the stage of diagnosis and treatment [55]. In addition, PA also reduces the side effects of treatment, especially deconditioning in cancer

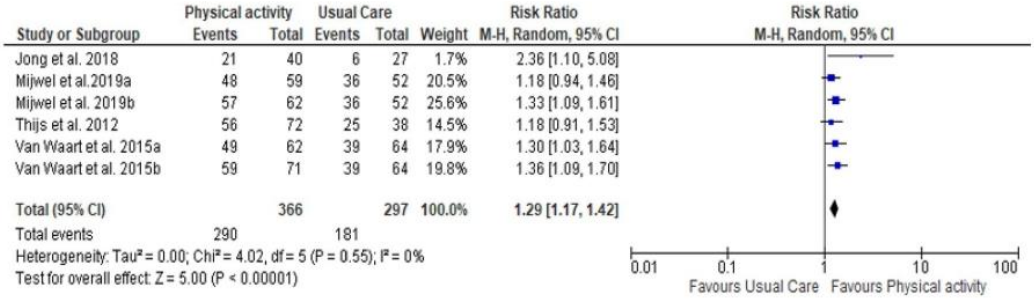

Fig. 3 Forest plot for comparison of the effect of physical activity versus usual care

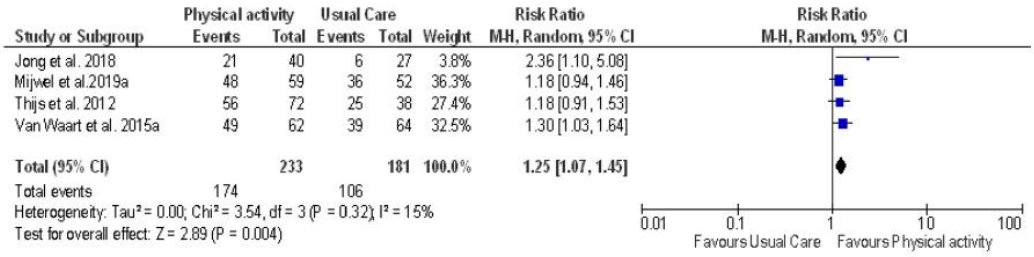

Fig. 4 Forest plot for comparison of the effect of physical activity versus usual care (excluding AT-HIIT and OnTrack interventions groups)

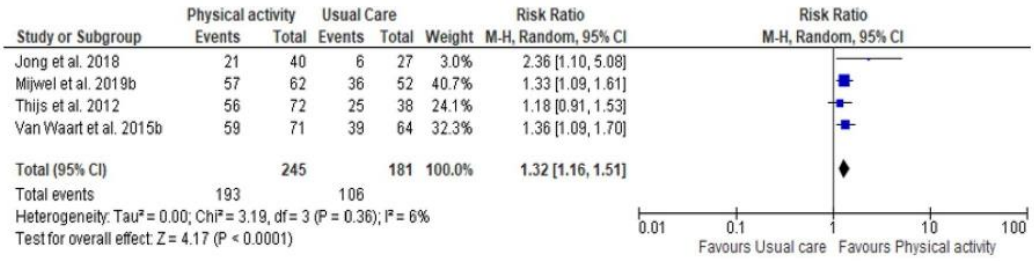

Fig. 5 Forest plot of comparison of the effect of physical activity physical activity versus usual care (excluding RT-HIIT and OncoMove intervention groups)

survivors by improving physical fitness [56]. Therefore, by improving these factors, PA also impacts RTW through its moderating effects. These explanations are consistent with the literature where studies showed that patients with a good quality of life returned to work earlier [5]. According to the type of cancer, most studies included breast cancer survivors, but other types of cancer comprising prostate cancer, colorectal, upper gastrointestinal, Hodgkin lymphoma and ovarian cancers were also included. The number of breast cancer studies could be explained by the fact that breast cancer is the most commonly diagnosed and prevalent cancer [1]. The included studies did not address some types of cancers (e.g., head and neck cancers, thoracic cancers, brain cancer, testis cancer, etc.). This could be explained by the fact that these cancers are rare or less frequent [1]. As stated by De Boer al.[17], is likely that the mechanisms of PA interventions are similar regardless of type of tumor, and thus cancer survivors with other types of cancer will experience the same benefits from the intervention aimed to improve RTW.

Our results revealed that the effective dose of PA on RTW in cancer survivors would be comprised between 7.6 METs.h/week and 15 METs.h/week, with an intervention duration of 16 to 20 weeks. These exercise doses respectively equate to 60 min per session of moderate-intensity aerobic exercise twice a week; and a combination of high intensity aerobic and resistance exercises, twice a week, lasting 50 min per session. The most effective exercise dose

for improving RTW was 15 METs.h/week, meaning that patients who participated in supervised aerobic and resistance exercise in a hospital setting were more likely to RTW. This can be explained by the motivation of the participants when the intervention was supervised and are consistent with the findings of a recent review which showed that combined aerobic and resistance training could improve common cancer-related health outcomes [57]. Similar results were found in the study by Zopf et al. [58] which reported that both aerobic and resistance training have a positive influence on a patient's physical, psychological and social level and should therefore be included in every exercise program.

The findings of this systematic review showed that PA interventions are still scarce and there is variability across interventions. As observed in previous reviews [14–16], the interventions varied widely in content and delivery. Some interventions were performed in a hospital setting, others at home or both in hospital and at home. A marked variability was also observed in the time at which interventions were deployed and their duration. The majority were deployed after completion of cancer therapy, while the others were deployed at different stages of treatment (e.g., before, before and during, during or after treatment). These results showed that PA interventions can be delivered to cancer survivors as supportive care throughout the course of the disease (post-diagnosis). However, to be more beneficial for patients, it is recommended to start PA intervention as early as possible after cancer diagnosis [10, 57, 59]. The same observation was made regarding the mode of delivery of the intervention. Most interventions were delivered with the supervision of physiotherapists, nurses, or other health professionals. The supervision consisted of leading the intervention and providing information or counseling to the participants. The variability in the design and implementation of PA interventions makes it difficult to recommend a specific exercise protocol for cancer survivors in the RTW intervention programs. Therefore, it is challenging to offer definitive recommendations on what constitutes an effective PA intervention to support RTW for cancer survivors [15]. Additionally, studies included in this review are lacking long-term follow-up, as they did not assess the long-term effects of PA interventions (more than 2 years). In our review, the longest follow-up time reported was 18 months after intervention. Even if we found that PA intervention has positive effects on RTW, questions about the long-term effects of PA on this outcome for cancer survivors remain unanswered. Therefore, it necessary to develop further intervention studies to explore these issues.

Another pitfall of this study is the lack of uniform definition of RTW across the studies. Return to work outcomes are multifaceted; they were measured by self-reporting in

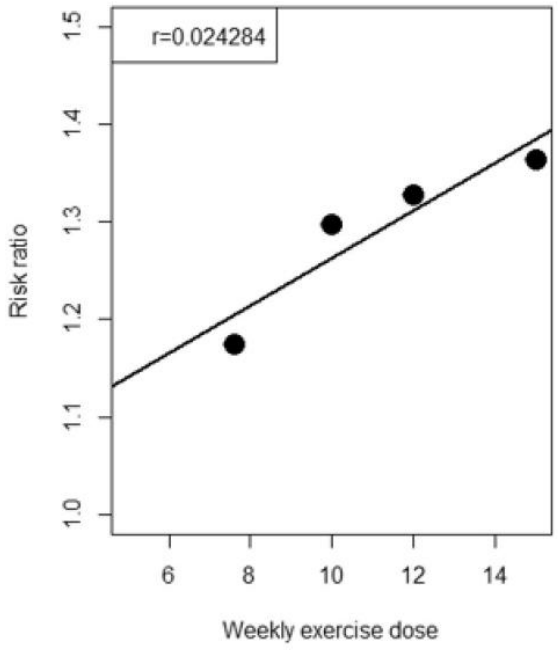

Fig. 6 Meta-regression between risk ratio and weekly exercise dose

all studies and varied from a continuous outcome (time to RTW) to a binary outcome (work status, work resumption, sick leave). Only 3 studies reported information on RTW as full-time or part-time work without provided more details on the meaning of RTW (i.e., return to the same job or a lesser job, to previous or new employment). The lack of clear definition of RTW could be justified by the fact that most included studies considered RTW as a secondary outcome. These results are in accordance with the literature [13, 16, 60]. As highlighted by Young et al. [61], RTW may involve returning to the pre-injury job, pre-injury employer, new employer, and work with or without accommodations as well as full-time or part-time. Therefore, it is needed for future researchers to clearly define what RTW means after cancer and choose the most suitable outcome measures.

Finally, all included studies compared the intervention to usual care as the control group. The usual care is defined as the care the targeted patient population would be expected to receive as part of the normal practice and, within RCTs, refers to the care the participants who are not receiving the tested intervention receive (i.e., without PA intervention) [62, 63]. We noticed that usual care is not the same across the studies and was not described. Yorganci et al.[62] reported that the usual care provided to patients is rarely described in detail in RCTs of a complex intervention [62].

Strength and Limitations of This Systematic Review

This systematic review process was conducted with a pre-registered protocol and reported in accordance with the PRISMA checklist (see Supplementary Table D) to ensure methodological quality. Furthermore, we completed a comprehensive and systematic search using four data collection techniques: search in bibliographic databases, grey literature, hand search through reference lists, and expert' consultation. This approach reduces the publication bias. We also used standard tools (Navigation Guide) specific to occupational and environmental health for assessing risk of bias in included studies. Finally, most of the included studies were RCTs, which are studies of high internal validity and constitute the gold standard to assess the effectiveness of interventions.

Like all studies, this review presents some limitations. First, the few studies included and the methodological weakness of some trials, especially the small sample sizes and lack of intention-to-treat analyzes. In addition, most of the studies included in this systematic review designed interventions without accounting factors associated with RTW such as sociodemographic and medical factors, location, and stage of tumors [64, 65]. This could explain the lack of statistically significant results in some RCTs. The final limitations concerned the generalization of results. The results of the study could not be generalized to all cancer survivors. This could be explained by the fact that most studies involved breast cancer survivors and all cancer types were not studied in our review. Additionally, the majority of patients included in the studies were those who have a sufficient physical fitness to participate in interventions, thereby excluding patients unable to participate in PA.

Recommendation for Future Research

This systematic review showed that PA has beneficial effects on RTW for cancer survivors. However, some research questions and limitations still exist and should be considered in future research. Thus, the following recommendations are provided to design and implement an effective PA intervention to support cancer survivors to RTW:

1. Provide a clear definition of the RTW outcome that will be evaluated using the most appropriate measures according to literature [16].
2. State the details of the intervention characteristics in terms of content, such as length, setting (hospital or home), timing (i.e., related to treatment), and mode of delivery (supervised or not).
3. Specifically, interventions should be designed and reported whilst taking the FITT characteristics of PA into account (e.g., frequency, intensity, time, and type) [66], that would allow an estimation of the exercise dose.
4. More specifically, future research should implement interventions based on PA recommendations for cancer survivors and investigate the long-term effects of PA and the dose–response relationship between PA and RTW [59].
5. To avoid the methodological limitations of studies, we recommended designing them using [16, 66]:

   - randomized clinical trials as the study design;
   - specific eligibility criteria: clearly stated eligibility criteria;
   - randomization of allocation groups (a description of the randomization method used to allocate patients into study groups should be provided);
   - provide more information (detailed description) about the content of care received by the control group;
   - pre-test the intervention with few participants, then pilot-test the intervention before to test the efficacy of the program;
   - blinding of outcome assessors; and
   - intention-to-treat analysis.

Conclusions

In conclusion, the current study provides the description of PA intervention and a comprehensive overview of the effects of PA on RTW in cancer survivors. When summing up, PA intervention studies aimed at supporting cancer survivors to RTW remain scarce. Of the included studies, we found variability across interventions in terms of content, mode, and timing. However, our results showed with moderate quality evidence that PA interventions are more effective than usual care in increasing the rate of RTW in cancer survivors. The PA interventions (aerobic and resistance exercise) with an exercise dose between 7.6 METs.h/week and 15 METs.h/week, consisting in 50–60 min per session of moderate to vigorous physical exercise, 2 twice a week seems relevant to improve RTW. For future research, recommendations on how to design and implement PA interventions to support cancer survivors' RTW have been proposed.

Deviations from Protocol

Deviations from the protocol are described below:

- Concerning search strategy, some health organization websites (International Agency for Research on Cancer,

European Cancer Organization and American Cancer Society) and grey literature websites (grey literature report) were not explored as we planned in the protocol.
- In the protocol, we planned to include observational studies. In the systematic review, we included only intervention studies (RCTs and nRCTs) because of their methodological quality.
- Disagreements in the study selection, data extraction, and risk of bias assessment steps were resolved by consensus rather than by a third author as specified in the protocol.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10926-022-10052-9.

Acknowledgements We would like to thank Colin Sidre and Catherine Weill, librarians at the University of Paris Medical School Library, for their valuable assistance and for reviewing the search queries. We would also like to acknowledge Elom Aglago and Yehadji Degninou for proofreading the final manuscript. We are grateful to the authors of the included studies notably Hanna Van Waart and Miek C. Jong, for providing the missing data. Finally, we would like to express our sincere gratitude to Dr. Sietske Tamminga and Dr. Angela de Boer for responding to our requests as experts.

Author Contributions TNW: conception and design of the study, screening of articles for eligibility, extraction and analysis of data, interpretation of data, drafting of the article and final approval of the version to be submitted. AN: screening of articles for eligibility, extraction of data, and participation in risk of bias and quality of evidence assessment. YR, AD, BP, AA-C and BE: conception and design of the study and coordination of the entire series of systematic reviews. BE: proofreading of final manuscript for language correction. All authors read and approved the final manuscript.

Funding This manuscript was prepared as part of the SIRIC ILIAD program supported by the French National Cancer Institute (INCa), the French Ministry of Health and the Institute of Health and Medical Research (Inserm); INCa-DGOS-Inserm_12558 contract. Têtê Norbert Wilson received a grant from the Togolese government and the non-profit organization Grain de Sel Togo, Inc. for his PhD research.

Data Availability The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethical Approval and Consent to Participate This study is exempted from ethics approval and patient consent since it is based on secondary data and does not directly involve human participants.

Consent for Publication Not applicable.

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2. Study 2. Synthesis and assessment of physical activity guidelines for cancer survivors

The study led to an article published in **"Supportive Care in Cancer".** It provided additional evidence on the benefits of PA and on the conditions for prescribing and implementing PA in cancer survivors. The key findings are summarized in four bullet points below.

Key findings in four bullet points

- There is strong evidence that **PA is safe, feasible**, and **can be prescribed** and practiced throughout the cancer treatment continuum (i.e., **before, during, and following cancer therapy**).
- All the guidelines recommended that **all cancer survivors should avoid inactivity**.
- They also recommend **prescribing PA taking into consideration any contraindications to PA**.
- regarding RTW outcomes, **no recommendation exists despite emerging evidence of the effectiveness of PA on RTW after cancer diagnosis**.

From this study, we highlighted that the existing PA guidelines are generic and did not provide guidance on how the PA can be implemented in practice. Future guidelines should be tailored to specific cancer types, at a particular phase of the cancer trajectory (i.e., prior, during, or after cancer treatment), and for specific outcomes including RTW.

Supportive Care in Cancer
https://doi.org/10.1007/s00520-023-08123-5

REVIEW

Physical activity in people diagnosed with cancer: a rapid review of recommendations and critical appraisal of international guidelines

Têtê Norbert Wilson[1,2] · Yves Roquelaure[1,3] · Bradley Evanoff[4] · Agnès Aublet-Cuvelier[5] · Bertrand Porro[1,6]

Received: 6 June 2023 / Accepted: 17 October 2023

Abstract

Purpose

There are numerous guidelines that recommend physical activity (PA) in people diagnosed with cancer, but the quality of these guidelines is unknown. The aim of this study was to identify existing PA guidelines for cancer survivors, describe the recommendations and assess their methodology quality.

Methods A rapid review of the literature was conducted in PubMed and EMBASE, supplemented by a search of the grey literature. The methodological quality of the guidelines was assessed using the AGREE II checklist. A descriptive synthesis of the recommendations from guidelines judged to be of good quality has been performed.

Results A total of nine guidelines published between 2006 and 2019 were included. Of nine guidelines, five achieved a high enough AGREE II score and were judged to be of good quality for use in clinical practice. We found that the recommendations from the five guidelines converged on the prescription of supervised PA (aerobic and resistance exercise) of at least 75 min per week of high intensity or 150 min per week of moderate intensity, spread over two to five sessions per week, equating to a PA dose between 8.70 and 17.5 MET.h/week. The recommendations were applicable to address the most common side effects of cancer and its treatment, namely fatigue, lymphedema, anxiety, depressive symptoms, health-related quality of life (QoL), survival, and physical function. However, no guideline recommends PA to improve other cancer-related outcomes, such as cognitive impairment, falls, sexual function, and peripheral neuropathy frequently experienced by cancer survivors. No guideline also referred to work outcomes (i.e., work ability, return to work, etc.).

Conclusion Most PA guidelines for cancer survivors are of good quality. However, specific PA guidelines are needed for a given cancer site (e.g., location, stage), at a particular phase of the cancer trajectory, and for specific outcomes including return to work (RTW) in order to tailor PA to each cancer survivor.

Keywords Cancer · Physical activity · Guidelines · Recommendations

✉ Têtê Norbert Wilson
tetenorbert.wilson@etud.univ-angers.fr

1 Univ Angers, Univ Rennes, Inserm, EHESP, Irset (Institut de recherche en santé, environnement et travail) - UMR_S 1085, IRSET-ESTER, SFR ICAT, F-49000 Angers, France

2 Grain de Sel Togo, Inc., Athens, USA

3 Univ Angers, CHU Angers, Univ Rennes, Inserm, EHESP, Irset (Institut de recherche en santé, environnement et travail) - UMR_S 1085, IRSET-ESTER, SFR ICAT, F-49000 Angers, France

4 School of Medicine, Washington University in St. Louis, St. Louis, USA

5 INRS (Institut National de Recherche et de Sécurité), Direction des Etudes et de la Recherche, 1 rue du Morvan, CS60027, 54519 Vandœuvre-lès-Nancy, France

6 Department of Human and Social Sciences, Institut de Cancérologie de l'Ouest (ICO), 49055 Angers, France

Introduction

Physical activity (PA) is one of the leading supportive care programs for the rehabilitation of cancer survivors [1–5], due to the growing evidence supporting its beneficial effects on the health of people diagnosed with cancer (i.e., physical, psychological, mental, and social health) [6–9]. As a result, several national and international organizations, scientific societies, and government agencies have developed guidelines that recommend PA to address the adverse effects of cancer treatment [10–13].

Guidelines are systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances [14]. However, developing high-quality guidelines is a complex task, requiring rigorous methodologies and adherence to standards (e.g., a systematic review of evidence, a multidisciplinary panel of experts and representatives from key affected groups, assessment of the benefits and risks of alternative care options) [15]. This results in the successful integration of recommendations into clinical practice. If developed and implemented in line with standards, guidelines offer a major advantage in improving the quality of care provided to patients by promoting evidence-based interventions [16, 17]. Guidelines can also improve the consistency of care by standardizing practices and supporting the implementation of high-value interventions [16]. Nevertheless, it has been reported that many guidelines suffer from methodological limitations and shortcomings in their development process [18, 19]. Regarding PA guidelines for cancer survivors, little is known about the extent of their development process and methodological quality. While Shallwani et al. [20] recently identified and assessed PA guidelines for people diagnosed with cancer, their study focused on guidelines with broader topics (e.g., cancer prevention, integrative therapy, nutrition, healthy lifestyles), but not return to work (RTW). The authors merely assessed the quality of the guidelines without describing the content of recommendations.

Furthermore, it has been revealed that many guidelines are not well implemented in practice [21]. Systematic reviews including PA interventional trials found heterogeneity in the implementation of PA programs across the included studies, in terms of time, period, setting, and mode of delivery of PA [22, 23]. In some studies, PA sessions were conducted at home [24], while in other cases, they took place in a hospital setting under the supervision of specialists [25–27]. Some studies implemented the PA programs before cancer treatment [28], and others during treatment [24, 25], or after the completion of treatment [26, 27, 29, 30]. This variability demonstrates the lack of standardization of care practices and adherence to PA recommendations, making it difficult to ensure clinical reproducibility of study results.

Considering these gaps, it is necessary to know the extent to which PA guidelines for cancer survivors have been developed and their quality. Knowledge of the quality of existing guidelines and identification of relevant recommendations facilitate the choice of interventions to be implemented in the field of cancer rehabilitation [20]. Therefore, this study aimed to identify guidelines that recommend PA for cancer survivors, describe the recommendations, and assess the methodology quality of guidelines.

Methods

Identification of guidelines

A rapid review has been conducted to identify guidelines that recommend PA for people diagnosed with cancer following the Cochrane rapid review methods [31]. Rapid review is a form of knowledge synthesis that provides evidence of the available research on a specific issue within a shorter time frame, assessing its methodological approaches as well as discussing existing gaps to provide future research directions [32, 33]. It is commonly used to develop clinical guidelines. The following databases were consulted on January 31, 2023, using keywords related to "Cancer," "Cancer survivors," "Physical activity," "Exercise," "Recommendations," and "Guidelines" and their synonyms (the search strategy is presented in Supplementary materials Table S1):

- Scientific electronic databases: MEDLINE/PubMed and EMBASE.
- General databases: Google Scholar.
- Cancer organizations websites: American Cancer Society, Canadian Cancer Society, British Cancer Research Institute, and the French National Cancer Institute.
- Specific guidelines databases: National Guideline Clearinghouse (Guideline Central) and the Alliance for the Implementation of Clinical Practice Guidelines (AICP).

Searches were conducted in the databases without restriction on the publication date.

Eligibility criteria

The guidelines were included if they (i) provided recommendations on at least one parameter of PA or exercise (Frequency, Intensity, Time, and/or Type), (ii) were designed for adult cancer survivors (≥ 18 years old), and (iii) were published in English or French. If two or more different versions of the same guideline existed, the most recent was considered. PA guidelines for the general population, pediatric cancer, prevention of cancer, and other chronic diseases (e.g., diabetes, cardiovascular diseases), as well as guidance documents or consensus statements that did not make explicit recommendations, or those without full text available, were excluded.

Selection of guidelines

Based on the eligibility criteria, guidelines were selected using the Covidence software (https://www.covidence.org/) [34] in three steps, as follows: (i) references downloaded and duplicates removed, (ii) titles and abstracts screed, and (iii) full text reviewed.

Data extraction

From each guideline, the data related to their characteristics were extracted as follows: (i) name of the organization and/or governing body that developed the guideline, (ii) year of publication, (iii) country, (iv) type of cancer, and (v) content recommendations of PA (including type, duration, intensity, frequency, and estimated dose). In addition, data related to the implementation of PA were extracted (i.e., time, period, setting, and mode of delivery), as well as specific considerations (i.e., precautions) before PA implementation.

Estimating the dose of PA

To quantify the total amount of PA recommended, the weekly dose of PA was estimated for each guideline as follows (terms in brackets represent units):

$$\text{Weekly dose of PA (in METs} \times \text{hours/week)} = \sum_{i=1} \textbf{Intensity}\ (\text{METs})_i \times \textbf{Duration}(\text{Hour})_i \times \textbf{Frequency}(\text{Session}/\textit{week})_i$$

MET: metabolic equivalent for task.

Quality assessment of guidelines

The Appraisal of Guidelines for Research and Evaluation, 2nd version

The second version of the Appraisal of Guidelines for Research and Evaluation (AGREE II) checklist has been used to assess the methodological quality of guidelines (i.e., rigor and transparency in which they included were developed) [35]. AGREE II is a validated and reliable instrument (Cronbach's $\alpha = 0.64$ to 0.88) [36, 37] widely used and internationally recognized for evaluating the methodological quality of guidelines in any area of healthcare or disease [38, 39]. It includes 23 items, each rated on a 7-point Likert scale (from 1 (strongly disagree) to 7 (strongly agree)), organized within six domains as follows: (1) Scope and purpose, (2) Stakeholder involvement, (3) Rigor of development, 4) Clarity of presentation, (5) Applicability, and (6) Editorial independence [36, 40]. Each domain captures a unique dimension of the guideline's quality and provides insight into the rigor of the guideline development process.

In addition, AGREE II also includes two global rating items (overall assessment). The first requires the appraiser to make a judgment on the overall quality of the guideline rating from "Low" to "High." The second asks whether the appraiser would recommend the guideline for use in practice, choosing: "Yes," "Yes, with modification," or "No."

Guidelines assessment process

Two appraisers (TNW and BP) independently evaluated each guideline included in the review using the AGREE II checklist. Any major discrepancies (≥ 3 points difference) in AGREE II item scores were resolved by discussion between the two appraisers. During this discussion phase, there was no disagreement between the two appraisers.

The standardized (weighed) mean scores for each domain (in percentage) were estimated using an automatic calculator (in Excel) developed by the Capacity Enhancement Program at McMaster University [41, 42]. The overall quality of guidelines was assessed based on the thresholds (cut-off score per domain) proposed by Molino et al. [43] as follows:

- *High quality:* standardized score ≥ 60% for domain 3 (*Rigor of elaboration*) and at least two other domains.
- *Moderate quality:* the standardized score for domain 3 is between 40 and 60%.
- *Low quality:* the standardized score for domain 3 is < 40%.

The global rate and overall quality of the guidelines allowed appraisers to indicate whether they (i) recommend the guideline for clinical practice, (ii) recommend the guideline but with modifications, or (iii) do not recommend the guideline. Guidelines considered and discussed in this study should be of *moderate* or *high* quality and recommended for practice (corresponding to a minimum global rate of 5 out of 7). Details of the quality assessment are presented in Table S2 and Table S3 (see supplementary tables). For this study, only the guidelines recommended for clinical practice were described and discussed.

Results

Characteristics of the guidelines

A total of 2034 records were identified from databases, including 1749 (86%) records identified from bibliographic databases and 175 (14%) records identified from other sources.

After removing the duplicates and applying the eligibility criteria, nine guidelines were included in the study (see Fig. 1) [11, 12, 44–50]. Seven guidelines were published between 2012 and 2019 [11, 12, 44–48], one in 2011 [50] and the remaining one in 2006 [49]. Five guidelines were published by organizations based in North America (Canada and the USA) [11, 12, 44, 48, 49], two in Australia [46, 47], and the two others in Europe (France and the Netherlands) [39, 44]. Six guidelines recommended PA for people diagnosed with all types of cancer [11, 12, 44, 46, 49, 50], one addressed the three most common types of cancer (i.e., breast, colorectal, and prostate cancers) [45], and one targeted people diagnosed with breast cancer [48]. One guideline did not specify the type of cancer covered [47]. The characteristics of the included guidelines are presented in Table 1.

Methodological quality of guidelines

The assessment of the methodological quality of guidelines is presented in Fig. **2.** The mean global rate was 5.60 (±0.88), ranging from 4.00 to 6.50. Based on the overall quality criteria, four guidelines met the quality threshold

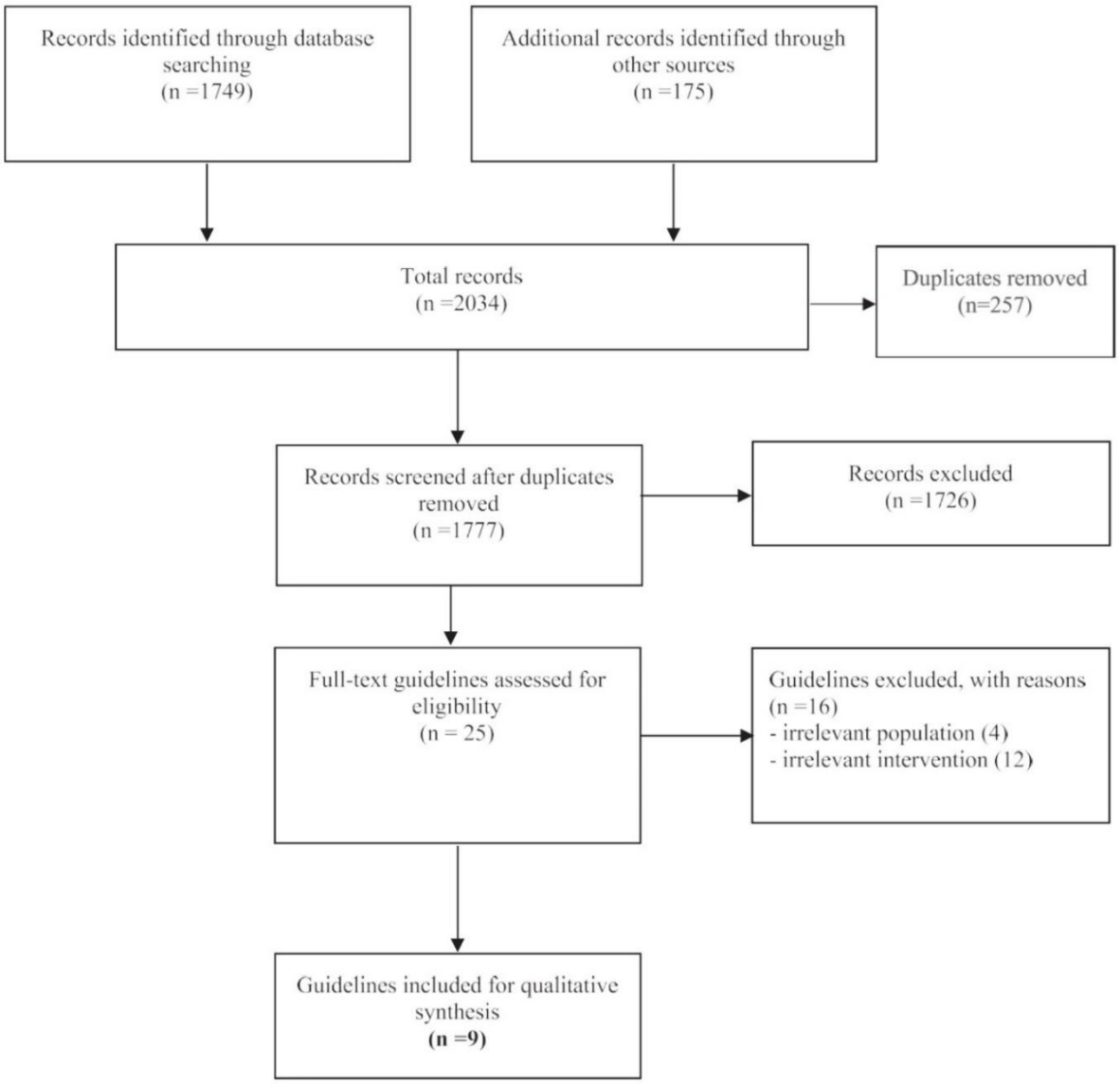

Fig. 1 Flow chart of the guideline selection process

with domain scores of ≥ 60% for rigor of development and at least two other domains and were judged to be of high quality [12, 44, 48, 50]. Four were of moderate quality [11, 46, 47, 49], and the remaining one was judged to be of low quality [45]. Finally, five guidelines with an overall score ≥ 5 out of 7, including one guideline of moderate quality and four of high quality, were recommended for clinical practice [12, 44, 46, 48, 50]. More details are provided below:

- Domain 1 (*Scope and purpose*) had the highest mean score (90% ± 9%) and was well developed for all the included guidelines (with scores/domain > 60%).
- Domain 4 (*Clarity of presentation*) had the second highest mean score (i.e., 72% ± 12%). Most of the included guidelines (n =7) were higher than the quality threshold of 60% for this domain, except the guideline by Cormie et al. [47] which received a lower score.
- Domains 2 (*Stakeholder involvement*), 3 (*Rigor of development*), and 5 (*Applicability*) have relatively low standardized mean scores (respectively: 51%, 59%, and 46%). However, four guidelines by Segal et al. [12], Campbell et al. [44], Brunet et al. [48], and Van den Berg et al. [50] scored high in domain 3 (≥ 75%).
- Domain 6 (*Editorial independence*) had a mean score of 71% (±21%) and its elaboration was good for five of the included guidelines [11, 12, 44, 46, 47].

Table 1 Summary of included guidelines characteristics

Characteristics	Number of guidelines
Year of publication	
2006–2010	7
2011–2019	2
Region or country of publication	
North America	5
Australia	2
Europe	2
Conditions for the implementation of PA	
Period (time)	
Before treatment	3
During and/or after treatment	5
Not reported	1
Supervision	
Supervised	8
Not reported	1
Mode	
Individualized	5
In group	2
Not reported	2
Types of cancer	
All types of cancer	6
Most frequent (lung, breast, colorectal)	1
Breast cancer	1
Not reported	1
AGREE II assessment	
Quality of guidelines	
High	4
Moderate	4
Low	1
Recommended for clinical practice	
Yes	5
No	2
With modifications	2

Abbreviations. *PA* physical activity, *AGREE II* Appraisal of Guidelines for Research and Evaluation instrument, 2nd version

Description of guidelines and PA recommendations

Only the five guidelines recommended for practice are described and discussed below [12, 44, 46, 48, 50]. Information on characteristics (type, duration, intensity, and frequency) and dose of PA, specific considerations, and benefits of PA are presented in Table 3.

Type of PA

Three guidelines, including two of high quality [12, 44] and one of moderate quality [46], recommended aerobic exercise combined with resistance exercise. One high-quality guideline recommended a combination of aerobic, resistance, and stretching exercises [48]. In addition, the guideline by Van Den Berg et al. [50] is in favor of aerobic exercises only.

Duration, intensity, and frequency of PA

Among the five guidelines recommended for practice, the three of high quality recommended performing 150 min of moderate-intensity PA, two to five sessions per week [12, 44, 50]. In addition, the high-quality guideline by Brunet et al. [48] recommended practicing PA by combining the three types of exercises: aerobic, resistance, and stretching exercises. According to the authors, PA in cancer survivors should comprise the following: (i) three sessions of aerobic exercise lasting 30 min each, and of moderate intensity per week; (ii) two to three sessions of low to high intensity of resistance exercise per week, without specifying the duration of each session; and (iii) three sessions per week of low intensity of stretching exercises lasting 50 to 60 min per session. Furthermore, Hayes et al. [46] developed a guideline of moderate quality that recommended three to five sessions per week of moderate-intensity exercise lasting 20 to 30 min per session.

	Domain	Guideline (author)									AGREE II mean score (± SD)
		Campbell et al. [44]*	HAS [45]	Hayes et al. [46]*	Cormie et al. [47]	Segal et al. [12]*	Rock et al. [11]	Brunet et al. [48]*	Van den Berg et al. [50]*	McNeely et al. [49]	
AGREE II Domain	1. Scope and purpose	89%	69%	89%	89%	100%	94%	97%	94%	86%	90% (±9%)
	2. Stakeholder involvement	53%	22%	44%	56%	86%	53%	36%	69%	39%	51% (±19%)
	3. Rigor of development	80%	19%	58%	45%	75%	46%	75%	77%	58%	59% (±20%)
	4. Clarity of presentation	83%	81%	94%	56%	75%	78%	92%	92%	69%	72% (± 12%)
	5. Applicability	52%	42%	54%	17%	52%	40%	40%	71%	48%	46% (±15%)
	6. Editorial independence	96%	42%	71%	96%	96%	75%	54%	54%	54%	71% (±21%)
Overall assessment	Global rate	5.50/7	4.00/7	5.00/7	4.50/7	6.50/7	4.50/7	5.50/7	6.00/7	4.00/7	5.60 (±0.88)
	Overall quality	High	Low	Moderate	Moderate	High	Moderate	High	High	Moderate	
	Recommended for clinical practice	Yes	No	Yes	RM	Yes	RM	Yes	Yes	No	

Fig. 2 Summary of AGREE II standardized and mean scores by domain and overall assessment of guidelines

Abbreviations and footnotes. *AGREE II* Appraisal of Guidelines for Research and Evaluation instrument 2nd version, *HAS* Haute Autorité de Santé, *SD* standard deviation, *RM* recommended with modification

*Guidelines recommended for clinical practice

The dose of PA

For all guidelines, we observed a variation in the weekly dose of PA ranging from 5.10 to 17.50 MET.h/week. For the five guidelines recommended for clinical practice, it was between 8.70 and 17.5 MET.h/week.

Conditions for implementing PA: period, setting, and mode of delivery

Three guidelines, including two of high quality [12, 50] and one of moderate quality [40], suggested performing PA during and/or after cancer treatment. The remaining two high-quality guidelines recommended that PA should be started as early as possible after cancer diagnosis [44, 48].

Regarding the supervision of PA, four high-quality guidelines recommended supervised PA in cancer survivors [12, 44, 48, 50]. The moderate-quality guideline by Hayes et al. [46] did not have any recommendation for the supervision of PA. Concerning the mode of delivery, two guidelines, including one of high quality [50] and the other of moderate quality [46], recommended PA be targeted and individualized to the health status of cancer survivors. By contrast, the high-quality guideline by Segal et al. [12] recommended delivering PA in a group consisting of a small number of patients and in a hospital setting [24]. Finally, two guidelines did not specify how PA should be delivered [44, 48].

Special considerations and safety precautions

All five guidelines recommended an initial medical assessment for each cancer survivor before starting PA [12, 44, 46, 48, 50]. The medical assessment can evaluate the patient's physical and cardiorespiratory conditions (e.g., by a 6-min walk test, exercise test) [44, 48, 50] and assess the comorbidities and contraindications to PA [12, 46].

Synthesis of results: benefits of PA

The five guidelines found with moderate and strong evidence that PA is beneficial to address physical and psychological symptoms due to cancer and its treatment, namely fatigue, lymphedema., anxiety, depressive symptoms, sleep disturbance, health-related QoL, survival, health bone, and physical function (e.g., muscle strength, physical condition, ability to task) [12, 44, 46, 48, 50]. They also showed that PA could be practiced at all stages of the disease (prior, during, or/and after treatment), but the benefits are greater if PA starts as soon as possible after the cancer diagnosis [44, 48]. No guidelines referred specifically to work outcomes (i.e., work ability, RTW, work retention, etc.).

Discussion

In this study, we found nine guidelines published between 2006 and 2019 by organizations or institutions located in developed countries (i.e., Australia, Canada, France, Netherlands, England, and USA) [11, 12, 44–50]. Five guidelines were judged to be of high quality and recommended for use in clinical practice [12, 44, 46, 48, 50]. They were described and analyzed. We also found that domain 1 (*Scope and purpose*) and domain 4 (*Clarity of presentation*) were the best developed for all guidelines and obtained the highest scores. However, two main methodological pitfalls were identified in the development of guidelines related to domain

Table 2 Description of physical activity guidelines and recommendations for people diagnosed with cancer

Guideline ID			PA characteristics (FITT and dose)	
Author, year of publication	**Institution (country)**	**Type of cancer**	**Type, intensity, frequency, and time**	**Dose of PA**
Campbell et al. (2019)	ACSM (USA)	All cancers	The guideline recommends all cancer survivors perform: aerobic and resistance exercise, of moderate intensity, 5 times/week (i.e., 3 sessions for aerobic exercise and 2 sessions for resistance exercise), 30 min/session. This equals a total of 150 min/week	9.50 MET.h/week
HAS (2019)	HAS (France)	The 3 most common cancers are as follows: breast, colorectal, and prostate	It is recommended to prescribe 150 min/week of aerobic and resistance exercise with moderate intensity, or 75 min/week of aerobic exercise, high intensity 3–5 days/week.	8.75 MET.h/week or 9.50 MET.h/week
Hayes et al. (2019)	ESSA (Australia)	All cancers	Guidelines recommend at least moderate intensity of aerobic and resistance exercise for approximatively 20–30 min per session. Exercise sessions should be spread across the week (3–5 sessions/week) avoiding 2 consecutive days	8.70 to 17.5 MET.h/ week
Cormie et al. (2018)	COSA (Australia)	Not specified	At least 150 min of moderate-intensity or 75 min of vigorous-intensity exercise each week, combined aerobic and resistance exercises, 2 to 3 sessions/week. Resistance exercise (e.g., lifting weights) involving the major muscles is recommended	8.75 MET.h/week or 9.50 MET.h/week
Segal et al. (2017)	CCO (Canada)	All cancers	The guideline consists of a minimum exercise recommendation: a goal of 150 min of moderate-intensity aerobic exercise spread over 3–5 days combining resistance exercise 2 days/week. Resistance exercise sessions should involve major muscle groups. Each session should include a warm-up and cool-down	9.50 MET.h/week
Rock et al. (2012)	ACS (USA)	All cancers	At least 150 min per week of moderate-intensity or 75 min per week of vigorous-intensity aerobic exercise 2 times/week	9.50 MET.h/ week

Table 2 (continued)

Brunet et al. (2012)	Canada	Breast cancer	PA programs for breast cancer survivors should include moderate aerobic training at least 3 times/week for 30 min, low-intensity of resistance training 2 to 3 times/week (6–12 exercises), and flexibility training 3 times/week for 50 to 60 min	12.05 MET.h/ week
Van den Berg et al. (2011)	CCCN (Netherlands)	All cancers	Moderate-intensity aerobic exercise, 5 times/week, 30 min/session. For a total of 150 min/week	10.00 MET.h/ week
McNeely et al. (2006)	Canada	All cancers	It is recommended that cancer survivors perform a combination of: - At least 20 min/session of aerobic exercise, 3 to 5 times per week of moderate intensity (e.g., 40–60% of heart rate reserve) - Resistance training should be performed 2–3 times per week, initially low and gradually increasing to one set of 20–25 repetitions, with a minimum of 48 h between training sessions to allow for recovery - Flexibility exercise should consist of 2 min/session performed 2 times/week	5.10 MET.h/week

Guideline ID	Conditions for implementation of PA	Special considerations and results	
Author, year of publication	**Period, setting (supervised, or not), and mode of practice**	**Specific considerations**	**Results and symptoms[a] or outcomes of interest**
Campbell et al. (2019)	PA should be initiated as soon as possible following cancer diagnosis. Supervised PA programs appear to be more effective than unsupervised or home-based programs. Exercise programs that were supervised appear to be more effective than strictly unsupervised or home-based programs	Cancer survivors should receive a comprehensive assessment for physical fitness before starting a PA program	Overall, the new guidelines recommended that people who have been treated for cancer should avoid inactivity **Benefits of PA:** anxiety, depression, fatigue, QoL, lymphedema, bone health, and physical function
HAS (2019)	PA may be initiated during and after cancer treatment. It should be individualized and tailored to the patient's physical condition and health status. Supervised APA programs tend to be more effective. PA in group, outside, in club, or association should be favored	Performed medical assessment (cardiovascular risk, comorbidities, contraindications) and assessed physical condition through simple tests before starting a PA program	All cancer survivors should avoid inactivity. The benefits of PA in cancer patients are greater than the risks. Fatigue should not be a barrier to participating in physical activity **Benefits of PA:** survival and recurrence of cancer, fatigue, QoL, physical condition, treatment-related side effects

Table 2 (continued)

Hayes et al. (2019)	PA can be initiated during and after cancer treatments. Appropriate exercise prescription for cancer patients needs to be targeted and individualized according to patients and cancer-specific considerations	Assess patient's condition prior to starting PA. Patient assessment, including the comorbidities, risk, severity of treatment-related toxicities, PA condition, and contraindications	Exercise is generally considered to be well tolerated during and following cancer treatment and is considered safe **Benefits of PA:** QoL, physical and psychological functions, survival, comorbidities, etc.
Cormie et al. (2018)	PA should be initiated prior to treatment. Exercise should be tailored to the individual's abilities and supervised by accredited exercise physiologists (the most appropriate health professionals to deliver exercise programs to cancer patients)	Not specified	All people diagnosed with cancer should avoid inactivity and should be as physically active as their current abilities and condition of health allow **Benefits of PA:** adverse physical and psychological effects (fatigue, physical function, QOL, psychological distress)
Segal et al. (2017)	It is recommended to initiate PA during or after completion of treatment. Exercise should be performed in a group under the supervision of a health care professional (as this provides greater benefit to patients)	Performed a pre-exercise assessment to evaluate any effects of disease, treatments, and comorbidities before starting exercise intervention	People living with cancer can safely engage in exercise while on active treatment or after completion of treatment **Benefits of PA:** QoL, muscle strength, physical condition, overall survival
Rock et al. (2012)	PA should be initiated as soon as possible following cancer diagnosis. PA should be individualized to the patient's condition and personal preferences. The presence of a caregiver or exercise professional during exercise sessions can be helpful (supervised PA)	Not specified	Exercise is safe and feasible during and after cancer treatment. All adult cancer survivors aged 18 to 64 should engage in regular PA, avoid inactivity, and return to normal activities **Benefits of PA:** cancer recurrence, overall and cancer-specific survival, lymphedema, comorbidities, physical condition, PRO[b]
Brunet et al. (2012)	PA should be initiated as soon as possible following cancer diagnosis Patients should participate in PA sessions supervised by a fitness professional	Performed pre-exercise medical assessment and exercise testing	Physical activity is safe and feasible and provides numerous physical and psychological health benefits **Benefits of PA:** several adverse effects including physical and psycho-social functions
Van den Berg et al. (2011)	Exercise should be tailored and individualized to the patient's disease characteristics (cardiopulmonary fitness levels) It is recommended that PA sessions be supervised as supervision provides motivation to all patients	Assessing the patient cardiopulmonary exercise testing by 6-min walk test before starting exercise	It is recommended to consider the patient's preferences, goals, and views regarding exercise

Table 2 (continued)

	PA should be performed as part of an outpatient program during the rehabilitation phase and immediately after treatment. Exercise sessions should be carried out under the supervision of an exercise physiologist to optimize the success of the program. The exercise program should be prescribed individually for each survivor	Perform exercise testing and initial medical assessment prior starting PA	Consider the needs, goals, and exercise preferences of the cancer patient. Identify any potential barriers to exercise, including long-term treatment and disease-related side effects that may compromise the ability to exercise **Benefits of PA:** fatigue, cancer rehabilitation[c]

Abbreviations and footnotes. *ACSM* American College of Sports Medicine. CCCN: Comprehensive Cancer Center the Netherlands, *CCO* Cancer Care Ontario, *HAS* Haute Autorité de Santé, *ACS* American Cancer Society, *ESSA* Australian Society of Exercise and Sport Sciences, *COSA* Clinical Oncology Society of Australia, *FITT* frequency, intensity, type, and time, *MET* metabolic equivalent of task, NA not applied, *PA* physical activity, *QoL* quality of life

[a]Symptoms: symptoms or health outcomes that are affected by PA

[b]PRO (patient-reported outcomes): includes fatigue, quality of life, psychological distress, anxiety, depression, and self-esteem

[c]Cancer rehabilitation: involves reducing or eliminating the side effects of cancer treatment and improving strength, functional ability, and quality of life in survivors [51]

2 (*Stakeholder involvement*) and domain 5 (*Applicability*), for which the majority of guidelines scored lower.

Firstly, in the majority of included guidelines, the views and preferences of the target population (i.e., cancer survivors) have not been sought (item 5 of domain 2) [11, 44–49]. These results corroborate previous studies [20, 52]. Indeed, many organizations recommend or require that guideline development groups include patient representatives or seek the views of the target population when developing guidelines [35, 53]. Stakeholder involvement is a key domain impacting the applicability of recommendations [54]. Research suggests that guidelines are more implementable or used when they address patient needs and preferences and include information to support patient involvement in decision-making [55]. A study by Pomey et al. [56] also highlighted the importance of patient involvement in decision-making about their care, particularly with the emergence of the Montreal model. According to the model, experiential knowledge acquired by the patient at diagnosis, during treatment, and throughout the survivorship is an essential element to be taken into account [56]. Nowadays, the inclusion of patients in scientific or medical consortia, as important stakeholders in health policies and research, is important for the researcher who is part of a logic of co-construction for the patient, with the patient. Favoring this co-construction makes the process of creating guidelines even more meaningful, as the reality experienced by patients is considered at the time of their development [56].

Secondly, concerning domain 5 (*Applicability*), eight guidelines received the lowest scores because they did not provide advice and tools/resources on how their recommendations can be implemented into practice [11, 12, 44–49]. In addition, there is a lack of information on guideline monitoring/and or auditing criteria, and the impact of their implementation in patients (economic assessment). Similar results were reported in the previous studies by Shallwani et al. [20] and Siedler et al. [52]. To improve the ability of end-users and practitioners to implement PA recommendations, guideline developers should provide specific information on the frequency, intensity, and duration of PA, as well as tools with concrete examples, to facilitate the implementation of recommendations [52].

Furthermore, we found that current PA guidelines for cancer survivors are generic and do not allow individualization of care. In their review, Buffard and colleagues also pointed out the same problem [57]. With the exception of guidelines by Brunet et al. [48] and the French National Authority for Health (HAS) [45], which respectively targeted people diagnosed with breast cancer [48] and the most frequent cancers (prostate, breast, and colorectal cancer) [45], the majority of guidelines were applicable to all cancer survivors regardless of the cancer location [11, 12, 44, 46, 47, 49, 50]. Whereas treatments and side effects vary according to the type and

stage of cancer, as well as the patient's characteristics (e.g., age, gender), each cancer survivor differs according to their needs and care pathways [58]. For example, some cancer survivors experience fatigue, while others suffer from diminished cognitive functioning and/or specific physical or psychological complaints [59]. Also, the needs of a 45-year-old cancer survivor are not the same as those of a 60-year-old. The same applies to stages of cancer (e.g., stage 4 versus stage 2 or 3) and cancer types (e.g., breast cancer versus lung cancer). Thus, at a time when treatment personalization (precision medicine) is seen as the future of cancer care, generic PA guidelines are not appropriate for cancer survivors.

Finally, findings from the five guidelines converged on supervised PA (aerobic and resistance exercises) of at least 75 min per week of high intensity or 150 min per week of moderate intensity, spread over 2 to 5 sessions/week, corresponding to an exercise dose between 8.70 and 17.5 MET.h/week [12, 44, 46, 48, 50]. These recommendations were applicable to address the most common physical and psychological side effects of cancer and its treatment. The guidelines also indicated that an initial medical screening should be performed to assess medical history, physical condition, comorbidities, and PA contraindications. A pre-existing medical visit is of great importance as it enables to take safety precautions and to tailor the program to the patient's health status [60].

None of the five guidelines recommend PA to improve other cancer-related outcomes frequently experienced by cancer survivors, such as cognitive impairment, falls, sexual function, and peripheral neuropathy [61]. This may be explained by the fact that there is insufficient or no evidence of the efficacy of PA for these outcomes (i.e., for cognitive impairment, sleep disturbance, others) at the moment the existing guidelines were developed. This explanation corroborates the results of the study by Campbell et al. [44]. Therefore, future research is necessary to develop valid PA guidelines in order to address these outcomes. In addition, no guidelines specifically addressed the question of the usefulness of PA to improve work outcomes (i.e., RTW, work capacity, etc.). Nevertheless, evidence of the effectiveness of PA in improving RTW as outcome in cancer survivors is emerging in the literature. For example, a recent systematic review and meta-analysis including eight randomized clinical trials showed evidence of the effectiveness of PA on RTW in cancer survivors [22]. The study also found that PA interventions (aerobic and resistance exercise) consisting of 50–60 min per session of exercise, moderate to vigorous intensity, and twice a week (i.e., a total of 100–120 min/week) are likely to enhance RTW. The PA threshold reported in this study is nearly equal to that set out in the PA Guidelines. The study also revealed interesting results regarding the dose effect of PA on RTW (i.e., 7.6 METs.h/week to 15 METs.h/week) and highlighted the need to develop specific guidelines to support this outcome in cancer survivors.

For the development of future guidelines, we propose expert consultations (stakeholder involvement), including rehabilitation physicians and oncologists, adapted physical activity professionals specializing in cancer, occupational physicians, and various stakeholders (e.g., patients, managers, physiotherapists, psychologists, caregivers).

Strengths and limitations of the study

The main strength of this study is that findings are based on high-quality guidelines, which is an advantage for their implementation in clinical practice. An additional strength is that the methodological quality of the guidelines was assessed using AGREE II, which is a valid and reliable tool recognized by the international scientific community. Finally, the quality assessment of each guideline was carried out independently by two appraisers, thereby reducing errors in guideline quality.

However, this study is subject to certain limitations, which are due to methodological choice (rapid review). The search strategy conducted in a few databases can lead to the omission of some key guidelines. Thus, the search may be less comprehensive, resulting in publication bias. In addition, limiting the inclusion of guidelines to those published only in French or English may result in language publication bias. Another limitation is that AGREE II did not provide clear instructions on how to interpret domain scores or specific thresholds for judging the quality of guidelines. The use of the 60% threshold remains arbitrary, although it is based on previous guideline assessments.

Conclusion

In this study, we identified nine guidelines recommending PA for people diagnosed with cancer and found that almost all were of good quality (moderate and high methodological quality). However, the current PA recommendations for cancer survivors are too general. More research is needed to develop valid guidelines for a given cancer site at a particular phase of the cancer trajectory, disease impact, and treatment side effects, and for specific outcomes (including RTW). Furthermore, future guideline developers should improve the applicability domain (domain 2) and involve patients and the target population representatives throughout the development process to enhance the quality, rigor, and trustworthiness of guidelines and their clinical use.

Supplementary Information The online version contains supplemen- tary material available at https://doi.org/10.1007/s00520-023-08123-5.

Author contributions TNW: designed and planned the study, developed the search strategy, screened guidelines for eligibility, extracted and analyzed the data, interpreted the results, and drafted the manuscript. YR, BE, AAC: designed and planned the study, coordinated all stages of the study, critically revised the methodological and scientific aspects of the manuscript. BP: designed and planned the study, contributed to the quality assessment of guidelines, critically revised the methodological and scientific aspects of the manuscript. All authors read and approved the final manuscript."

Funding This manuscript was prepared as part of the SIRIC ILIAD program funded by the French National Cancer Institute (INCa), the French Ministry of Health, and the Institute of Health and Medical Research (Inserm), INCa-DGOS-INSERM-ITMO Cancer_18011.

Têtê Norbert Wilson received a scholarship from the Togolese government and the non-profit organization Grain de Sel Togo, Inc., for his Ph.D. research.

Declarations

Ethical approval and consent to participate Ethical approval and patient consents are not required for this study as it is based on second- ary data and does not directly involve human participants. The study was conducted in accordance with the ethical standards of the National Consultative Ethics Committee, the 1964 Declaration of Helsinki, and its subsequent amendments or comparable ethical standards.

Competing interests The authors have no conflicts of interest to dis- close in relation to the content of this article.

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3. Study 3. Guidance for prescribing and implementing adapted physical activity program to support return to work in breast cancer survivors

The final step of this chapter is the study 3 which involved combining findings from systematic review and evidence-based guidelines to make a guidance for prescribing and implementing PA programs to support RTW in breast cancer survivors. This study led to an article that will be submitted for publication. The key messages arising from this study are summarized as follows:

Key messages

What is already known about this subject?

From the results of study 1, we now know that there is evidence for the effectiveness of PA in improving RTW in cancer survivors. However, there is no PA guidelines that referred to RTW outcome.

What are we proposed?

In absence of existing PA guideline concerning RTW in cancer survivors, and as it has been suggested that future guidelines should be tailored to specific cancer types, we proposed in this study a guidance with practical protocols for prescribing and implementing adapted physical activity program to support RTW in breast cancer survivors. As such, we proposed:

- **100 to 120 minutes per week of aerobic and resistance exercise with moderate to vigorous intensity (at least 4.5 METs).**
- Exercise should be spread over 2 to 3 times a week for at least 12 to 20 weeks.
- Prior to start PA programs, **it is necessary to perform medical and pre-exercise assessments.**
- PA should be **initiated as soon as possible following cancer diagnosis**, **under the supervision of physical exercise professional**, and in hospital setting.

How might this impact on clinical practice?

This study allowed to develop protocols with clear and practical examples that facilitate their use in clinical practice by HCPs and physical exercise professional, as well as by patients and their relatives.

Practical protocols for prescribing and implementing adapted physical activity program to support return to work in breast cancer survivors

Têtê Norbert Wilson *[,1,2], Yves Roquelaure[1,3], Bradley Evanoff[4], Agnès Aublet-Cuvelier[5], Bertrand Porro[1,6]

[1]Univ Angers, Univ Rennes, Inserm, EHESP, Irset (Institut de recherche en santé, environnement et travail) - UMR_S 1085, IRSET-ESTER, SFR ICAT, F-49000 Angers, France

[2]Grain de Sel Togo, Inc., Athens, USA.

[3]Univ Angers, CHU Angers, Univ Rennes, Inserm, EHESP, Irset (Institut de recherche en santé, environnement et travail) - UMR_S 1085, IRSET-ESTER, SFR ICAT, F-49000 Angers, France

[4]Washington University in St. Louis, School of Medicine, USA.

[5]INRS (Institut National de Recherche et de Sécurité), Direction des Etudes et de la Recherche, 1 rue du Morvan, CS60027, 54519 Vandœuvre-lès-Nancy, France

[6]Department of Human and Social Sciences, Institut de Cancérologie de l'Ouest (ICO), 49055 Angers, France

***Corresponding Author**

Têtê Norbert Wilson, tetenorbert.wilson@etud.univ-angers.fr

ORCID ID: https://orcid.org/0000-0003-1696-7454

Abstract

There are several guidelines that recommend PA to mitigate the treatment related side effect in cancer survivors. Nevertheless, none of the existing recommendations can be applied to support the return to work (RTW) in cancer survivors. The aim of this preliminary study was to propose practical protocols for the prescription and implementation of adapted physical activity (APA) program to support RTW in breast cancer survivors. The protocols have been developed following a three-phase procedure (i) phase of evidence synthesis, (ii) phase of discussions with APA expert; and (iii) phase of validation. After these steps, we validated a prescription of 100 to 120 minutes per week of aerobic and resistance exercise with moderate to vigorous intensity (at least 4.5 METs) to support breast cancer survivors in returning to work after diagnosis. Exercise should be spread over 2 to 3 times a week for at least 12 to 20 weeks. Prior to start PA programs, it is necessary to perform medical and pre-exercise assessments. PA program should be initiated as soon as possible following cancer diagnosis, under the supervision of physical exercise professional, and in hospital setting.

Background

Physical activity (PA) is one of the main supportive care programs recommended by several guidelines to improve most of physical and psychological side effects experienced by cancer survivors [1–4]. A recent rapid review summarizing existing PA guidelines for cancer survivors showed that PA can be safely practiced following a cancer diagnosis, before, during, or/and after treatment to address a variety of cancer health-related outcomes (e.g., fatigue, anxiety, depression, function, and quality of life, etc.) (study 2 of the thesis). However, none of the existing guidelines recommend PA to improve the return to work (RTW) of cancer survivors, whereas a recent systematic review and meta-analysis showed with moderate evidence that PA interventions have significant positive effect on RTW in cancer survivors [5]. Breast cancer was the most studied cancer, by more than half of the included studies.

The rapid review also revealed that the current guidelines are generic and did not provide guidance (advice and/or tools) on how the recommendations can be implemented (study 2). As such, there is a need to develop specific PA guidelines for a specific cancer site (i.e., at least for the most common cancers), at a particular phase of the cancer trajectory (i.e., prior, during, or after cancer treatment), and for specific outcomes including RTW, in order to tailored PA to each cancer survivors. Therefore, in the absence of existing PA recommendations concerning RTW, this preliminary study aims to propose practical protocols for the prescription and implementation of adapted physical activity (APA) program to support RTW in breast cancer survivors.

Explanation of mechanisms of physical activity on return to work after a cancer diagnosis

Although our systematic review found that PA improves RTW after cancer diagnosis, it is necessary to know the underlying mechanisms. Better knowledge of mechanisms by which PA acts positively on the RTW after cancer would help healthcare practitioners (HCPs) to develop appropriate PA programs to address and improve most of the problems experienced by cancer survivors during their RTW process. In the literature, various mechanisms underpin

the beneficial effect of PA on RTW after cancer diagnosis. In this section, we present a brief explanation of these mechanisms.

The beneficial effects of PA on RTW could be explained through physiological and biological mechanisms. Evidence from many studies showed that PA acts on cancer outcomes through its effects on biological markers involved in cancer progression and on the physiological functions of cancer survivors [6–13].

These include:

- reducing cancer-related inflammation,
- reducing levels of hormones (insulin, estrogen, growth factors, and others),
- regulating cancer metabolism,
- improving muscular (muscle hypertrophy) and immune functions,
- improving physiological functioning of cardiorespiratory, cognitive, and brain and nervous systems.

It has been shown that PA has the potential to disrupt the vicious circle of chronic inflammation induced by cancer [14–16]. Long term exercise training (moderate and high intensity) significantly reduced the level of pro-inflammatory cytokines [14,17–22], which contribute to the experience of pain [23], cognitive impairment [24], fatigue [25], and neuropathy [26] in cancer patients. The reduction in inflammatory markers with exercises may occur indirectly through improved endothelial function, reduced body weight, or increased insulin sensitivity [11]. and consequently improve muscular function [27–29]. With regard to immune function, multiple favorable changes in the immune system have been reported in cancer survivors who participated in PA programs. It has been shown that during exercise, the concentration of immune cells (e.g., cytotoxic natural killer, lymphocytes, monocytes, neutrophils, and tumor-associated macrophages) increases dramatically in circulation [16]. By reducing inflammatory markers and improving immune function, PA reduces cancer-related fatigue (CRF) and improves quality of life (QoL) in patients diagnosed with cancer [30], thereby improving RTW in cancer survivors [31]. Furthermore, it has been

shown that PA improves physiological functions in cancer survivors (i.e., cardiorespiratory, neuromuscular, cognitive, and nervous systems functioning) [6,32–35].

Through the biological and physiological pathways, PA impedes tumor progression and proliferation [36,37] and induces physical, physiological, and psychological effects [1,38]. By producing these effects, PA may enhance RTW in cancer survivors. The explanation of this hypothesis is based on integrative and transactional conceptual models of the RTW proposed by Porro et al. [39]. Indeed, Porro and colleagues have recently developed an integrative model (REWORK BC Model) in which the physical and psychological determinants or factors of RTW in breast cancer survivors are presented [39]. The links between the determinants as well as factors on which interventions could act to improve RTW are also explained in the model. However, there is strong evidence that PA have beneficial effect on most of the factors involved in the model [34,40–46].

It has been shown that cancer survivors who participate in exercise interventions generally improve their cardiorespiratory fitness (i.e., VO2peak) and muscle strength [47–49]. This contributes to counteracting physical deconditioning and reducing CRF, thereby reducing the relative effort required to complete daily living activities [42]. In patients with various cancer types, PA was associated with significantly reduced body mass index (BMI) and body weight [6]. These results were in line with the systematic review by Keogh and MacLeod [50], which showed with strong and moderate evidence that exercise resulted in improvement in physical fitness (i.e., aerobic endurance, muscular strength and endurance), body composition (i.e., lean muscle, body fat mass, body weight), functional performance (i.e., walking and sit to stand speed) in prostate cancer patients.

It has also been shown a significant association between PA, depression and cognitive function in cancer survivors [16,51]. Specifically, the authors showed that aerobic and resistance exercises reduced depressive symptoms and cognitive impairment in patients diagnosed with cancer, and these effects were associated with an improvement of learning, memory, and attention difficulties; as well as executive function [51]. Similar results were reported by an umbrella review which found that aerobic and resistance exercises have beneficial effects on

mental health, general well-being, and QoL, in people undergoing and recovering from cancer [42]. These results are consistent with a recent review of 36 systematic reviews, meta-analyses, and RCTs [43] which found that PA reduces fatigue, anxiety, and depression; improves QoL, thereby allowing patients to perform their daily activities without difficulty [43]. By improving these physical, physiological, and psychological outcomes which are predictors of RTW [39,52–54], it seems obvious that PA may improve RTW outcomes in cancer survivors (i.e., work ability, work status, RTW, time to RTW).

In sum, this section highlighted the absence of direct effect of PA on RTW after a cancer diagnosis. However, PA acts on biological and physiological markers involved in cancer progression. Through these mechanisms, PA improves most of physical and psychosocial outcome associated with cancer therapy, and consequently contributes to improve RTW in cancer survivors (via a mediation effect). The beneficial effects of PA on RTW may be mediated through a reduction of chronic inflammation, metabolic and sex hormones, improvement of immune function, as well as its beneficial effects on physical, physiological, and psychosocial outcomes. A summary of all mechanisms is presented in an integrative diagram (**see Figure 1**).

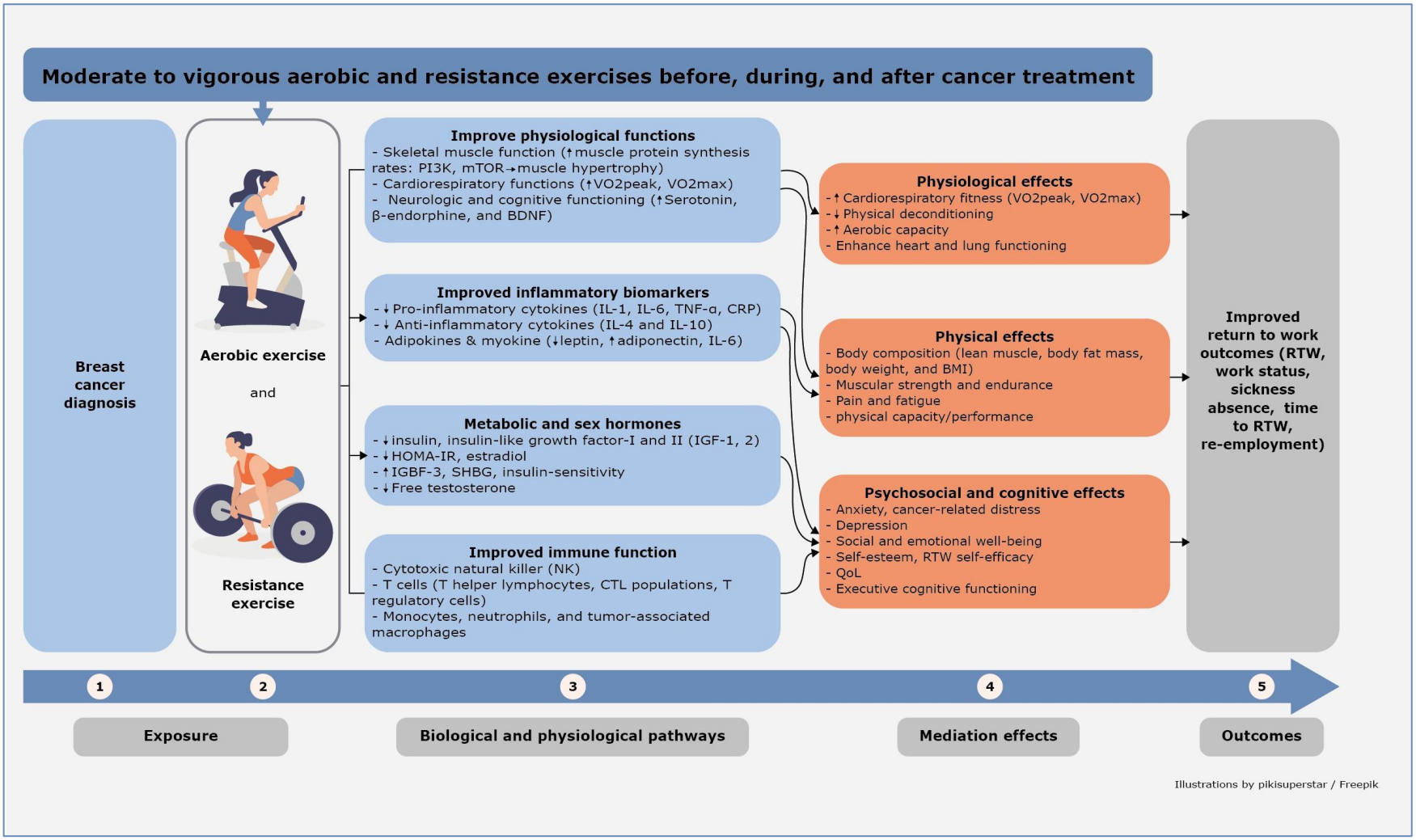

Figure 1. An integrative illustration of various mechanisms linking beneficial impact of physical activity and return to work in cancer survivors.

Adapted from Friedenreich et al. [17], Matei et al. [27], and French National Institute of Health and Medical Research (Inserm) collective expertise report [55].
Abbreviations. BDNF: Brain-Derived Neurotrophic Factor, BMI: body mass index, CRP: C-reactive protein, HOMA: Homeostasis Model Assessment, IGBF-3: Insulin-like Growth Binding Factor Protein-3, IGF-1: insulin-like growth factor-I, IGF-2: insulin-like growth factor-II, IL-1: interleukin-1, IL-10: interleukin-10, IL-6: interleukin-6, mTOR: mechanistic target of rapamycin, PI3K: phosphoinositide-3-kinase, SHBG: sex hormone-binding globulin, TNF-α: tumor necrosis factor-α, VO2max: Maximum oxygen consumption or uptake.

Prescription of adapted physical activity to support return to work in breast cancer survivors: practical protocols for use in clinical practice

- **The choice of breast cancer**

The choice to focus the protocols on breast cancer is justified by the fact that breast cancer is the most frequently diagnosed cancer worldwide, with an estimated 2.3 million new cases (11.7% of all cancers) in 2020 [56]. It is also based on the findings of the previous studies. Most of studies included in our systematic review (study 1) involved breast cancer patients. In addition, the results of study 2 suggested to tailor future PA recommendations to a specific cancer site, as existing guidelines are too generic.

- **Procedure for developing protocols**

Protocols are series of procedural steps or consensual rules with a precise sequence of activities to be adhered in order to manage a specific clinical condition [57–60]. Protocols are usually based on guidelines and/or organizational consensus and provide a locally agreed standard to which clinicians and the organization can work. Thus, our protocols are developed following Standards for Clinical Practice Guidance (National Clinical Effectiveness Committee, 2015) and a step-by-step guide to developing protocols proposed by the Modernization Agency and the National Institute for Clinical Excellence to support the development of protocol-based care [61]. To develop protocols, we followed a three-phase procedure: (i) preparation phase; (ii) discussions with experts; and (iii) validation of the final protocols.

Phase of preparation

The preparatory phase corresponds to the period during which the two studies were carried out. It included a systematic review aimed at providing the evidence for the efficacy of PA on RTW (study 1) and the identification of existing PA guidelines for cancer survivors (study 2). The results from both studies were used to propose a first version of protocols, which was submitted to the expertise of a physical exercise professional experienced in cancer care.

Phase of discussion and validation

The initial version of protocols was discussed and amended during meetings attended by the APA professional, a psychologist specializing in RTW after cancer, and a researcher. The APA professional and the psychologist have more than 10 years' experience. During the meeting which lasted 2 hours, a summary of the finding of previous studies is presented, followed by a presentation of protocols. Then, the protocols are discussed and amended based on the feedback and experience of experts. Following the discussions, modifications were applied to the first version of the protocols, leading to a final version of protocols that has been proposed and validated.

- **Prescription of exercise program: clinical approach and final protocols**

Prior to prescribing PA to support RTW in breast cancer survivors, some prerequisites, or specific considerations such as exercise testing, assessment of exercise contraindication, as well as preferences and needs of patients should be taken into account. Thus, the following pre-exercise assessments and protocols have been validated.

Medical assessment and exercise testing

Given the different medical conditions experienced by cancer survivors, it is therefore necessary to require medical clearance (i.e., approval from a medical professional to engage in exercise) before starting a PA program, to ensure no cardiac or other contraindications to PA. In addition, cancer survivors should receive a comprehensive assessment of all components of health-related physical fitness (i.e., cardiorespiratory fitness, muscle strength and endurance), and some specific precautions (e.g., beware of fracture risk, etc.), to individualize an exercise prescription. The exercise testing may be administrated by an physical exercise professional following the American College of Sports Medicine (ACSM) guidelines for exercise testing and prescription [62] or their national equivalent. Conducting these baseline assessments is valuable for determining the risks and contraindications of exercise.

Preferences or interests of patients

Exercise is only effective in improving clinical outcomes if the patient "completes the script" (follows the exercise program). As such, to facilitate long-term adherence to exercise training, it is crucial

to consider the needs and exercise preferences of cancer patients prior to prescribing an exercise program. In this case, the HCPs should communicate clear and detailed information about the safety of PA as soon as the cancer diagnosis is established. They should also discuss with patients to understand their needs. Particularly for those on sick leave, it is very important to discuss about their work and desire to RTW.

Exercise prescription

Once medical and fitness assessments have been completed, an exercise professional can prescribe an individualized (tailored) PA program for the patient. From a scientific perspective (i.e., based on studies results), the effective dose of PA that significantly improves RTW in breast cancer survivors is comprised between 7.6 and 15 METs-h/week. This corresponds to a PA program of:

- ✓ 100 to 120 minutes per week of aerobic and resistance exercise with moderate to vigorous intensity (at least 4.5 METs).
- ✓ Exercise should be spread over 2 to 3 times a week for at least 12 to 20 weeks.

In order to achieve the 7.6-15 METs-h per week, the following protocols have been validated based on the core components of PA (i.e., frequency, intensity, time, and type of exercise) (see Table 1). The protocols will assist the HCPs and exercise professional to design a safe and effective exercise program to support RTW of breast cancer survivors. In clinical practice, metabolic equivalent (METs) can be estimated from a Compendium of physical activities [63].

Table 1. Detail of protocols for prescribing adapted physical activity to support return to work in breast cancer survivors.

Exercise parameter (FITT)	Before treatment (pre-habilitation)	During treatment	After treatment
Aerobic exercise			
Frequency	2 days/week	2-3 days/week	2 days/week
Intensity	Moderate to vigorous (≥4.5 METs): 50-85% VO_2R or HRR; or RPE 12-18	Moderate (4.5-6 METs): 40-60% VO_2R	Vigorous: 60-85% (≥6 METs)
Type (mode)	Dynamic, rhythmic activities involving lower or upper body such as treadmill walking, cycling, and arm ergometer	Dynamic, rhythmic activities involving lower or upper body such as treadmill walking/jogging, cycling, stepper, elliptical, and arm ergometer	Rhythmic and prolonged activities involving whole body such as brisk walking, cycling, aerobic dancing, rowing, vigorous calisthenics, lap swimming for fitness
Time (duration)	40-50 minutes/session	45-60 minutes/session	30-45 minutes/session
Resistance exercise			
Frequency	1 day/week	1 day/week	1 day/week
Intensity	Moderate to vigorous (≥4.5 METs): 50-85% of 1-RM; RPE 13-17	Moderate (4.5-6 METs):	Moderate to vigorous (≥4.5 METs): 50-85% of 1-RM; RPE 13-17
Type (mode)	Circuit weight training, free weights, resistance bands, or resistance balls, involving all major muscle group (legs, hips, back, chest, abdomen, shoulders, and arms)	Fixed weight machines, resistance bands, handheld weight, or bodyweight exercise involving all major muscle group	Prolonged exercise involving whole body: sitting or stand-up rowing machines, deadlift
Time (duration)	20-30 minutes	20-30 minutes	20-60 minutes

Adapted from Wonders et al. [64], Stefani et al. [65], Campbell et al. [1], and the American College of Sports Medicine [62]. HRpeak: peak heart rate; HRR: Heart Rate Reserve; VO2R: Volume of oxygen reserve; VO2peak: oxygen uptake; RM: repetition maximum; RPE: rating of perceived exertion on a 6-20 Borg scale; MET: Metabolic Equivalent of Task.

Exercise before cancer treatment

The main goal of exercise in pre-habilitation is to decondition cancer patients or prepare them for the enormous stress imposed by cancer treatment, in the hopes of mitigating its physiological and psychological side effects [66]. As such, the initial sessions serve to develop aerobic capacity, strength, endurance, and motivation, as well as build up engagement for longer exercise. During

this phase, exercise intensity levels should be adapted to the current health status and physical fitness of patient (without falling below 4.5 METs) [65].

Exercise during cancer treatment (for individuals undergoing treatment)

During treatment, the role of exercise is to alleviate or prevent the acute and long-term side effects of cancer treatment (i.e., reduced pain, lymphedema, fatigue, anxiety, and improve body composition) and improve treatment tolerance. Ideally, for an individual undergoing cancer treatment, the prescription will include a whole-body workout that targets all the major muscle groups (Wonders, 2012). Cancer patients may continue their pre-habilitation exercise program, even if the intensity may need to be decreased during treatment. Progression should consist of increases in frequency and duration rather than in intensity [64].

Exercise after cancer treatment

The overall goal of exercise programs after cancer therapy should be to prevent cancer recurrence, to return the former level of physical function (e.g., daily living activities), and increase survival. Exercise helps improving physical and psychosocial function, as well as QoL and work outcomes (e.g., RTW), by mitigating the long-term and late side effects of treatment (i.e., reduced fatigue, anxiety, depressive symptoms, increased physical function) and preventing associated morbidities (i.e., diabetes, cardiovascular diseases, and obesity) [66]. During this phase, the progression should consist of increase in intensity of exercise.

- **A practical example of exercise program prescription**

A practical example of exercise prescription is provided bellow.

Table 2. Sample weekly exercise program for cancer patients.

Day of week	Before treatment	During treatment	After treatment
Monday	Aerobic exercise (e.g., treadmill or arm ergometer) of moderate intensity (40%-60% HRR) for 40 minutes	Aerobic exercise of moderate intensity for 45 minutes	Aerobic exercise (e.g., brisk walking, rowing) of vigorous intensity (60-85%) for 30 minutes
Tuesday	Day off	Day off	Day off
Wednesday	Continuous moderate intensity (40%-60% HRR) of aerobic exercise for 40 minutes	Aerobic exercise of moderate intensity for 45 minutes	Aerobic exercise (e.g., brisk walking, rowing) of vigorous intensity (60-85%) for 30 minutes
Thursday	Day off	Day off	Day off
Friday	Resistance exercise (e.g., free weight or body weight) of vigorous intensity for 30 min	Resistance exercise (e.g., free weight or body weight) of moderate intensity for 30 min	Resistance exercise (e.g., sitting, or stand-up rowing machines) of moderate intensity for 50 minutes
Saturday	Day off	Day off	Day off
Sunday	Day off	Day off	Day off

Adapted from Stefani et al. [65].

- **Guidance for implementing physical activity**

The implementation of guidelines or protocols into clinical practice is challenging because they do not deal with the many logistical issues that arise in clinical practice. Below, we propose guidance for implementing the protocol, answering following questions often asked during the implementation of the directives.

When (time related to treatment), how (under supervision or not), and where (setting) cancer survivors should exercise?

When (time): although PA can be practiced at any time after diagnosis (i.e., before, during or after treatment), we propose to initiate exercise programs as early as possible (i.e., soon after cancer diagnosed). Early adherence to exercise programs leads to greater benefit.

How (mode of delivery: under supervision or not): supervised exercise programs appear to be more effective than strictly unsupervised or home-based exercises. Cancer survivors who perform supervised exercises have greater adherence and better results than those perform self-monitored exercises. Therefore, we propose that, when possible, cancer survivors practice PA under the supervision of physical exercise professional experienced in cancer care. These specialists can appropriately apply protocols to maximize the safety and efficacy of exercise for patients with cancer, even with or minimal adverse effects.

Where (setting): the most appropriate settings to carry out a supervised PA program are medical settings. Indeed, a supervised exercise program would offer services that are delivered in formal medical settings, such as inpatient and outpatient rehabilitation units, exercise facilities housed within medical settings, primary care settings, and palliative or hospice care units [67]. After treatment completion or at the end of the program, patients can continue individual exercise at home or in a fitness centers.

Follow-up (evaluation)

During the implementation of PA programs, it is crucial to assess the physical fitness of the patient at least one time. This may help to adapt exercise intensity to the patient's capacity. Medical follow-up is also advised during this period. Follow-up should focus on the cardiovascular, psychological, and biological parameters [65]. The assessment of these parameters should be regular, approximatively every 2 months and the results obtained allow to verify the adhesion to the program, the absence of symptoms related to a possible reduction of exercise tolerance [65]. Furthermore, RTW outcomes should also be assessed every 6 months from the end of the exercise program. The long-term effect of PA program can also be evaluated by measuring sustainable RTW outcomes.

Conclusion and future directions

This study allowed understanding the mechanisms by which PA acts on RTW after cancer diagnosis. Based on evidence and expertise of physical exercise professional, this study proposed practical protocols for exercise prescriptions to support RTW in breast cancer survivors. These protocols can be used by HCPs, pending the development of future guidelines.

The main strength of this study is that protocols are proposed based on the synthesis of evidence (i.e., systematic reviews and evidence-based guidelines). This demonstrates the strength of the statements in protocols. In addition, protocols are based on the expertise of a physical exercise professional experienced in cancer care, allowing us to take into consideration the difficulties of implementation in clinical practice. Although the protocols are proposed based on evidence synthesis, the methodology used to develop them remains limited compared with that recommended for the development of guidelines. Nevertheless, they represent a first proposition and could therefore be used pending the development of future guidelines following standard methods.

Finally, we have not been able to test the applicability and use of the protocols in clinical practice. However, future research is needed to implement and evaluate them.

Author contribution

Têtê Norbert Wilson: planned, designed the study, and drafted the manuscript.

Yves Roquelaure, Bradley Evanoff, Agnès Aublet-Cuvelier: contributed to design and plan the study, coordinated all stages of the study, and provided critical revision of the final manuscript.

Bertrand Porro: contributed to the conceptual design, critically revised the methodological and scientific aspects of the manuscript.

Funding

This manuscript was prepared as part of the SIRIC ILIAD program funded by the French National Cancer Institute (INCa), the French Ministry of Health and the Institute of Health and Medical Research (Inserm), INCa-DGOS-INSERM-ITMO Cancer_18011.

Têtê Norbert Wilson received a scholarship from the Togolese government and the non-profit organization Grain de Sel Togo, Inc. for his Ph.D. research.

Data Availability

Not applicable

Compliance with ethical standards

Competing interests

The authors have no conflicts of interest to disclose in relation to the content of this article.

Ethical approval

Ethical approval and patient consent are not required for this study as it does not directly involve human participants. The study was conducted in accordance with the ethical standards of the National Consultative Ethics Committee, the 1964 Declaration of Helsinki and its subsequent amendments or comparable ethical standards.

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CHAPTER 5: GENERAL DISCUSSION

The general discussion is complementary to those presented in the three articles included in this thesis. It presents the summary of the main findings of the thesis, interprets, and discusses these findings with existing literature. Then, the strengths and limitations of the thesis are outlined. The chapter ends with implications of the thesis for research and practice and recommendations for further research.

In this thesis, we evaluated the effects of PA on RTW after cancer diagnosis and provided evidence of its effectiveness on RTW of cancer survivors. To achieve this main objective, we specifically 1) assessed the effectiveness of PA interventions on RTW in cancer survivors and determined the dose of PA needed to improve this outcome (study 1); 2) identified existing guidelines that recommend PA in people diagnosed with cancer, described the recommendations, and assessed their quality (study 2); and lastly, merging the results of the two studies, 3) in absence of existing recommendations concerning RTW in breast cancer survivors specifically, we proposed guidance with practical protocols for prescribing and implementing adapted physical activity program to support RTW in breast cancer survivors (study 3). To address the thesis objectives, we used a methodology based on evidence synthesis.

1. Summary and interpretation of main findings

The first study has several key findings. First, we found from narrative synthesis that supervised PA interventions including aerobic and resistance exercises, delivered during and/or after cancer therapy improved RTW in cancer survivors. This result is in line of a scoping review by Guo et al. (Guo et al., 2021), which reported that physical exercise is effective and HCPs can utilize it to enhance RTW in cancer patients. Secondly, based on the meta-analysis, we found an overall pooled RR of RTW of 1.29 (95% CI: 1.17, 1.42) in cancer survivors who participated in the PA interventions. These results revealed that PA interventions had a significant positive effect on RTW after cancer diagnosis compared to usual care. Furthermore, the meta-regression highlighted a positive linear relationship between PA dose and RTW outcomes. Thus, we found that an exercise dose between 7.6 METs-h/week and 15 METs-h/week seems appropriate to improve RTW in cancer survivors. This corresponds to 100-120 minutes per week of moderate to vigorous exercise, spread

two times a week. Taken together, the findings of the first study provide with moderate evidence that PA interventions are more effective than usual care in improving RTW in cancer survivors.

To date, only two systematic reviews and meta-analyses have addressed the effectiveness of rehabilitation interventions to enhance RTW outcomes in cancer survivors (Algeo et al., 2021; de Boer et al., 2015). Although not directly comparable, the meta-analysis by de Boer et al. (de Boer et al., 2015) that focused on different types of intervention showed with moderate quality evidence that multidisciplinary interventions involving physical, psycho-educational and/or vocational components led to higher RTW rates than care as usual (RR 1.11, 95% CI 1.03 to 1.16, n = 450 patients). Similar results were reported in another review by Algeo et al. (Algeo et al., 2021). In contrast, de Boer and colleagues suggested with low quality evidence that physical training was not more effective than care as usual in improving RTW (RR 1.20, 95% CI 0.32 to 4.54) (de Boer et al., 2015). However, it is important to note that this result is limited to only one RCT of breast cancer patients, with a small sample size (n=28 patients). Compared to de Boer's study, our systematic review included eight clinical trial that exclusively concerned PA.

About the type of PA, our results were consistent with other studies that evaluated the impact of PA interventions in cancer survivors and found that PA interventions consisting of resistance and aerobic exercises significantly improve health-related outcomes experienced by cancer survivors (Campbell et al., 2019; De Luca et al., 2016; Dieli-Conwright et al., 2018; Milne et al., 2008; Mok et al., 2022; Mutrie et al., 2007; Smith, 2016). These findings mean that aerobic and resistance exercises combined, in a supervised manner, resulted in greater benefits for cancer survivors than programs consisting of only one mode of exercise or usual care (Mok et al., 2022). This may result from the physiologic and psychological advantages of the combined resistance and aerobic exercises. Indeed, it was demonstrated that aerobic exercise mainly improved cardiorespiratory fitness, cardiovascular endurance by increasing oxygen uptake (VO2), while resistance exercise mainly improved the muscle strength by increase muscle mass (Irwin, 2013; Sözen, 2018; Wilmore, 2003). Aerobic and resistance exercises were also associated with improvement of fatigue, HRQoL, mental health, as well as work performance and work ability, which are predictors of RTW after cancer diagnosis (Courneya et al., 2007; Dieli-Conwright et al., 2018). Thus, it is

plausible that the synergy of the combined actions of these two types of exercise produced a greater effect than that of a single mode of exercise.

Statistical heterogeneity refers to the degree of dissimilarity in the results of individual studies (i.e., variability in the intervention effects among the included studies). Although we highlighted some variability in content and implementation of PA interventions, our meta-analysis showed no statistical heterogeneity across the included studies ($I2=0\%$, $P<0.05$). Heterogeneity is an important consideration when performing a systematic review (Lo et al., 2019). It allows to analyze the degree of variability (e.g., clinical, methodological, and statistical) among the individuals studies included. Also, heterogeneity is a key factor in the assessment of the certainty of the evidence (Guyatt et al., 2011) and the consistence of the evaluated effectiveness of interventions (Walker et al., 2008). As such, investigating heterogeneity is a major challenge for judging the effectiveness of interventional exercise trials in cancer patients (Carayol et al., 2015). It can be the opportunity for understanding and interpreting the effects of the intervention provided by meta-analysis (Higgins and Thompson, 2002). Therefore, in our meta-analysis, the lack of statistical heterogeneity suggests that the variability observed in PA interventions has little or no influence on exercise efficacy (e.g., RRs varied little across studies) and showed the consistency of individual study results.

In the study 2, we identified nine guidelines that recommended PA for cancer survivors and were developed in different countries, including France. Of these, five are of high quality and recommended for use in clinical practice. However, the guideline developed by the French institution (Haute Autorité de Santé: HAS) was not included in the five guidelines because of its low methodological quality. This raises the question of its application in clinical practice. Therefore, there is a need to develop a valid French guideline that complies with the standards.

We highlighted that PA is safe, feasible, and well-tolerated for cancer survivors. We also found that PA can be prescribed and practiced throughout the cancer treatment continuum (i.e., before, during, and/or after cancer therapy). The guidelines supported to tailor PA to preferences, needs, and abilities of cancer patients. However, the benefits are greater if exercise is performed under the supervision of exercise professionals. These findings are supported by other systematic reviews

and meta-analyses (De Lazzari et al., 2021; Großek et al., 2023; Heywood et al., 2017; Singh et al., 2018), which reported that the safety and feasibility outcomes were similar, irrespective of exercise mode, supervision, duration, or timing, as well as the type and stage of cancer (Singh et al., 2018). The feasibility outcomes were determined by computing recruitment rate, withdrawal rate, reason for withdrawals, and exercise adherence rate.

Concerning the supervision of exercise, our results are consistent with previous individual patient data meta-analysis of 34 RCTs (n= 4519 cancer patients) which reported that exercise effects on cancer and treatment-related side effects were significantly larger for supervised than unsupervised interventions (Buffart et al., 2017). A more recent meta-analysis including 20 RCTs also supported our results (Baumann et al., 2022). This may be attributed to the fact that exercise supervision provides greater motivation for patients and facilitates their adherence to programs (D.-W. Kang et al., 2022; Kraemer et al., 2022).

Lastly, all guidelines recommend avoiding inactivity after cancer diagnosis. They also recommend exercise to address several physical and psychological symptoms due to cancer and its treatment. However, the existing PA guidelines are not applicable to support cancer survivors in their RTW process. These results suggest the need to develop future guidelines to address RTW outcomes in cancer patients.

The third study of the thesis proposed a guidance with practical protocols for prescribing and implementing an adapted physical activity program to support RTW of breast cancer survivors, as there is evidence for the effectiveness of exercise in improving RTW after the diagnosis of this type of cancer. It was based on the merged results from studies 1 and 2 (evidence-base findings), combined with the expertise of a physical exercise professional. Discussions with the expert led to a consensus to propose protocols according to the three main phases of the cancer treatment continuum (pre-habilitation, during, and after). As such, we proposed:

- 100 to 120 minutes per week of aerobic and resistance exercise with moderate to vigorous intensity (at least 4.5 METs).
- Exercise should be spread over 2 to 3 times a week for at least 12 to 20 weeks.

- Prior to start PA programs, it is necessary to perform medical and pre-exercise assessments PA should be initiated as soon as possible following cancer diagnosis, under the supervision of physical exercise professional, and in hospital setting.

Practical examples of prescribing and implementing the PA programs were also provided.

2. Strengths and limitations of the thesis

This section focuses on the overall strengths and limitations of the studies presented in this thesis. The thesis presents several key strengths. The main strength is the use of the highest evidence-based methods (standard methods) to answer the research question.

For the first study, the main strength was its rigorous methodology. In this study, we have tried to conduct a comprehensive and transparent review following PRISMA guidelines (Page et al., 2021). Before starting, the review protocol was registered on PROSPERO. After formulating the research question and defining the eligibility criteria, we followed the main steps to conduct a systematic review (i.e., research strategy, studies selection, data extraction and synthesis, risk of bias and quality assessment) (Tawfik et al., 2019). We searched eligibility studies in more than five medical databases using approximately 30 keywords whilst imposing no restrictions on language and publication dates. The searches were supplemented by the grey literature search, the hand-search and experts' consultation. These approaches reduced publication and language bias. The entire search strategy was proofread and reviewed by a librarian. Two review authors independently reviewed records for inclusion, extracted data, and performed a risk of bias assessment using a standard form that was developed and tested until the authors reached convergence and agreement. Disagreements between authors were resolved by discussion. We documented the reasons for exclusion of the full text articles. In addition to systematic review, we performed meta-analysis. Furthermore, we assessed the overall quality of the evidence using GRADE criteria. Therefore, we think that we have done our best. All these methods ensure a systematic and rigorous synthesis of evidence, reduce biases, and maximize transparency.

The overall limitation of the first study concerned the applicability of findings of review to Low- and Middle-Income Countries (LMICs) and to other types of cancer. Indeed, the systematic review

considers studies and patients from the developed countries of North America and Europe. Social security systems and labor markets in these countries differ considerably from those in LMICs, as well as the professional trajectories following cancer diagnosis. However, when generalizing the results to another country, the potential effect of a particular country's social security system should still be considered. Also, for the generalization of the results of this review to countries outside Europe or the USA, cultural differences regarding employment and cancer disclosure should be taken into account (de Boer et al., 2015). With regard to the type of cancer, breast cancer was the most studied, followed by prostate, colorectal, Hodgkin lymphoma, and gynecological cancers. We did not find any studies that were aimed at patients with lung cancer (despite being common in cancer survivors of working age) (Jakubowska, 2023; Naghibzadeh-Tahami et al., 2022) nor aimed at less prevalent cancer diagnoses including brain cancer, bone cancer, and other gastro-intestinal cancers. In addition, studies of non-solid cancers were not included. However, long-term and late effects of specific treatments for specific cancers, such as solid versus non-solid tumors, may differ and play a role in the RTW process (Stein et al., 2008). Therefore, the generalization of the review's results to these types of cancer should be made with caution.

The second study complemented the findings of the first one by providing evidence on how prescribing and implementing PA in cancer survivors. The study was performed using the Cochrane rapid review methods recommendations(Garritty et al., 2021). The major advantage of conducting the second study is that it provides additional findings on the beneficial effects of PA in cancer survivors, which greatly contributed to the design and conduct of study 3. Specifically, it provided clear additional results on exercise prescription and implementation (from PA recommendations). Moreover, it helped to determine the quality of existing PA guidelines, facilitating their choice for use in clinical practice by HCPs.

Nevertheless, one of the main limitations of the second study was the incompleteness of search (e.g., use fewer databases or limit the language) and a single reviewer for screening guidelines. This could lead to a potential bias or error in the selection process (Moons et al., 2021).

Both studies 1 and 2 provided the evidence and findings that enabled to develop a practical guidance for prescribing and implementing APA program to support RTW in breast cancer survivors.

The main strength of study 3 was that the protocols are proposed not only based on literature evidence, but also from the expertise of a physical exercise professional. However, its key limitation is the lack of additional time to be able to test the applicability of the protocols in clinical practice. Future work is needed to better understand the protocols, including implementation and evaluation.

3. Contributions and implications of the thesis

This doctoral thesis has many contributions and implications for research and clinical practice, as well as for cancer survivors. To the best of our knowledge, this thesis is the first that evaluated the effects of PA on RTW after a cancer diagnosis and provided evidence of its effectiveness on RTW outcomes. It is also the first to determine the dose of PA needed to improve RTW in cancer survivors.

The findings of this thesis based on an evidence-based approach, fill gaps of the existing literature on the beneficial effects of PA to improve RTW after cancer diagnosis. As such, the thesis strongly contributes to the literature by providing additional evidence for the benefits of PA in cancer survivors. Another contribution of the thesis was the quantification of PA (in term of exercise dose and FITT components of PA). Indeed, the thesis has shown the optimal dose and the type of PA appropriate to improve RTW outcomes among cancer survivors. This result may help clinicians to better prescribe PA, because prescribing the correct dosage of a drug or intervention is important for achieving the desired therapeutic efficacy and avoiding undesired effects (Milone and Shaw, 2009). It may also help researchers to design new interventional studies (RCTs) aimed at assessing the effectiveness of PA on RTW after cancer diagnosis.

Furthermore, the thesis contributed to gaining additional evidence of the beneficial effects of PA in cancer survivors. Specifically, study 2 provides evidence on safety and feasibility of PA through cancer treatment continuum. It also provides recommendations on how prescribe and implement PA to support cancer patients. These findings could be useful to exercise professionals and clinicians when prescribing PA.

The proposition of practical protocols in study 3, contributes to bridging the current lack of PA guidelines applicable to RTW after cancer. The protocols, along with practical example for exercise

prescription and implementation, can be used by physical exercise professionals, rehabilitation specialists, HCPs, and community educators to design and deliver exercise programs that best meet the needs, preferences, and abilities of cancer patients.

For cancer survivors, the greatest benefit that could be achieved by protocols is to improve health outcomes, specifically the RTW. Protocols can also improve consistency of care, as their use in clinical settings allow to standardize patient care. Protocols empower patients to make more informed healthcare choices about PA programs, and to consider their personal needs and preferences when selecting the best option (Woolf et al., 1999).

Lastly, for policy-makers in France, the results of this thesis provide additional arguments in favor of developing policies to promote APA and reimburse expenses related to PA programs in cancer patients.

4. Perspectives and recommendations for future research

Although the present thesis provides evidence for the effectiveness of PA on RTW after cancer and has several contributions and implications, it also provides a basis for further research. The following recommendations are provided for conducting future research:

1- While we have shown that PA improves RTW in cancer survivor, the effects of PA on sustainable RTW or work retention (more than 28 days after initial RTW) are unknown. All the clinical trials included in our systematic review often considered the initial phase of RTW and have not examined the lasting outcomes (i.e., sustainable RTW or job retention) after the period of work resumption. The RTW process may be of longer duration and one's initial RTW may not always be successful or enduring (Brusletto et al., 2018). Assessing the sustainable RTW is crucial for understanding the long-term effect of PA programs (van Egmond et al., 2016). Therefore, future studies aimed at assessing the effects of PA on sustainable RTW are warranted. Studies on other types of cancer, specifically non-solid cancers are also needed.

2- Although we have explained the mechanisms by which PA acts on RTW after cancer, these mechanisms remain little documented, as they are not based on a systematic review.

Moreover, to date, there are no empirical studies conducted exclusively with the aim of investigating the mechanism underlying the effect of PA on RTW. As such, high quality, systematic review aimed at understanding the mechanisms by which PA acts on RTW are needed to fill these evidence gaps. Causal inference studies with mediation analysis (to assess factors mediating the effect) are also needed. Finally, qualitative studies are recommended to better understand these mechanisms.

3- In our study, we highlighted that there are no PA guidelines applicable to support RTW of cancer survivors. These findings suggest the need to develop future PA guidelines at national or international level that would be applicable to address RTW after cancer. Future guidelines may be elaborated following standards for developing trustworthy clinical practice guidelines (Institute of Medecine, 2011; Laine et al., 2011). More specifically for France, high-quality PA guidelines for cancer patients (to address RTW and other outcomes) are warranted.

Conclusion

Findings from studies conducted in this thesis demonstrated that PA is more effective in improving RTW in cancer survivors compared to usual care. The thesis also helped to determine the dose of PA needed to improve RTW in cancer survivors. In sum, this thesis provides moderate evidence for the effectiveness of PA on RTW outcomes in cancer survivors. This is additional evidence of the beneficial effects of PA in cancer patients.

Furthermore, recommendations from PA guidelines for cancer survivors stated that PA is safe and feasible through the course of cancer treatment. As such, PA could be prescribed to any cancer patent before, during, and/or after treatment following recommendations. Therefore, guidance with practical protocols has been proposed to assist HCPs and exercise professionals prescribe and implement PA programs to support RTW in cancer survivors. We have not been able to test the applicability and use of these protocols in clinical practice. This project would benefit from future research into the application and evaluation of the proposed protocols.

Résumé en français

1. Introduction

Le cancer constitue un problème majeur de santé publique, avec plus de 19 millions de nouveaux cas diagnostiqués dans le monde en 2020 (OMS, 2022 ; Wild et al., 2020). Le dépistage précoce du cancer et les avancées thérapeutiques ont contribué à augmenter le nombre de personnes diagnostiquées pour un cancer et améliorer leur survie (Shahid et Raza, 2023). En 2020, le nombre de survivants du cancer était estimé à 50,6 millions, et ce nombre devrait augmenter dans les années à venir (CIRC, 2020). Parmi les survivants du cancer, près de la moitié sont en âge de travailler et sont en emploi au moment du diagnostic (Ferlay et al., 2018 ; Miller et al., 2019). Cependant, le cancer et ses traitements ont des effets négatifs sur la santé physique, psychologique et mentale des patients (Grusdat et al., 2022 ; Stein et al., 2008). Par exemple des effets secondaires physiques (ex., fatigue, douleur), émotionnels et psychologiques (anxiété et dépression) causés par le cancer et ses traitements ont été rapportés chez survivants du cancer (Baden et al., 2020 ; Götze et al., 2020 ; Jefford et al., 2017). Ces symptômes peuvent persister pendant plusieurs mois ou années après le traitement, impactant négativement la qualité de vie globale et les activités quotidiennes des survivants du cancer (Schmidt et al., 2019 ; Taskila et Lindbohm, 2007). En outre, il a été démontré que le cancer et ses traitements entraînent des répercussions négatives sur la capacité de travail (Horsboel et al., 2015) et la vie professionnelle des survivants du cancer (Blinder et Gany, 2020 ; Thandrayen et al., 2022). Plus précisément, environ 26 à 53 % des employés diagnostiqués et traités pour un cancer sont en arrêt-maladie, quittent ou perdent leur emploi après le diagnostic et ils rencontrent des difficultés à reprendre le travail (D. Kang et al., 2022 ; Mehnert, 2011 ; Park et al., 2008). Une étude réalisée par de Boer et al. (de Boer et al., 2009) a montré que les survivants du cancer ont 1,4 fois de risque d'être au chômage que les personnes en bonne santé. Même 1 à 2 ans après le diagnostic, seuls 39 à 77 % des survivants du cancer sont en mesure de reprendre le travail (Paltrinieri et al., 2018). Ces résultats montrent que tous les survivants du cancer ne reprennent pas le travail après un diagnostic de cancer et qu'ils rencontrent souvent des difficultés sur le marché d'emploi (Rottenberg et al., 2016). Pourtant le non-retour au travail ou le chômage a des impacts sur les patients atteints

de cancer (ex., perte de revenus) (Hernandez et Schlander, 2021), sur leurs familles et sur la société (ex., pensions d'invalidité et perte de productivité) (Meadows et al., 2010 ; Shakespeare, 2018). Compte tenu de tous ces problèmes rencontrés par les survivants du cancer, et en particulier des difficultés liées au retour au travail (RAT) après le diagnostic du cancer, il est donc nécessaire de les soutenir dans leur processus de RAT.

Plusieurs études notamment des revues systématiques, méta-analyses et études observationnelles ont montré que l'activité physique (AP) améliore la majorité des effets secondaires physiques et physiologiques liés au cancer et ses traitements (Loprinzi et Cardinal, 2012 ; Myers et al., 2018 ; Piraux et al., 2020 ; Schwartz et al., 2017). Plus précisément, l'AP réduit la fatigue liée au cancer (Belloni et al., 2021 ; X. Chen et al., 2023 ; Kessels et al., 2018), améliore la condition cardiorespiratoire et la qualité de vie des survivants du cancer (Joaquim et al., 2022 ; Martínez-Vizcaíno et al., 2023). Il a également été démontré que l'AP améliore la force musculaire, la composition corporelle (masse grasse/masse maigre) et l'image corporelle des patients (Padilha et al., 2017 ; Reis et al., 2023), ainsi que leur l'estime de soi (Landry et al., 2018). Chez les femmes diagnostiquées d'un cancer du sein au stade précoce, l'AP a été associée à une meilleure qualité de vie, à une réduction de la dépression et de l'anxiété, et à une diminution des effets indésirables du traitement adjuvant (Vehmanen et al., 2022). Une récente étude incluant des essais contrôlés randomisés (ECR), des revues systématiques et des méta-analyses a montré avec des preuves solides que les AP de type aérobique et de résistance améliorent les symptômes couramment associés au cancer et ses traitements, notamment l'anxiété, les symptômes dépressifs, la fatigue, les fonctions physiques et la qualité de vie liée à la santé (Campbell et al., 2019). Ces résultats confirment les preuves des effets bénéfiques de l'AP sur la fonction physiologique, la santé physique et psychologique des survivants du cancer.

Bien que le RAT soit une préoccupation importante pour les employés ayant survécu au cancer, les preuves de l'efficacité de l'AP sur le RAT après un diagnostic de cancer restent incertaines (de Boer et al., 2015). En effet, à ce jour, seules quelques études dans la littérature ont examiné l'effet de l'AP sur la RAT chez les survivants du cancer (Björneklett et al., 2013 ; Groeneveld et al., 2013 ; Hubbard et al., 2013 ; Lee et al., 2017 ; Leensen et al., 2017 ; Van Waart et al., 2015). Les résultats de ces études primaires sont souvent contradictoires et limités parce qu'elles portent sur des

échantillons de petite taille (c'est-à-dire peu de participants) et sont de qualité limitée (Algeo et al., 2021 ; Bilodeau et al., 2017 ; Hoving et al., 2009 ; Rosbjerg et al., 2021). Il est donc difficile d'établir des preuves consistantes sur l'efficacité de l'AP sur la RAT après un cancer. De plus, le type d'AP le plus approprié et la dose d'AP en termes de durée, fréquence et d'intensité nécessaires pour améliorer le RAT restent inconnu. De nouvelles études sont donc nécessaires pour combler ces limites. Par ailleurs, les preuves des effets bénéfiques de l'AP sur les symptômes associés au cancer ont conduit à l'élaboration de directives recommandant l'AP comme soins de support pour atténuer les effets secondaires liés au traitement des cancers (Buffart et al., 2014 ; Campbell et al., 2012 ; Harris et al., 2012 ; Mustian et al., 2012 ; Segal et al., 2017). Cependant, la qualité méthodologique des directives reste inconnue, et il n'est pas certain que les recommandations issues de ces directives soient applicables pour améliorer le RAT chez les survivants du cancer.

Pour combler les limites identifiées dans la littérature, l'objectif de cette thèse est d'évaluer les effets des programmes ou des interventions d'AP sur le RAT chez les survivants du cancer et d'apporter les preuves de l'efficacité de l'AP sur le RAT après un diagnostic de cancer. Pour atteindre l'objectif principal, nous avons défini les trois objectifs spécifiques suivants :

Objectif 1 : évaluer l'efficacité des interventions d'AP sur le RAT chez les survivants du cancer et déterminer la dose d'AP nécessaire pour améliorer le RAT.

Objectif 2 : le deuxième objectif est d'identifier et évaluer la qualité méthodologique des directives qui recommandent l'AP chez les personnes diagnostiquées d'un cancer.

Objectif 3 : enfin, sur la base des résultats des deux études, proposer un guide avec des protocoles pratiques pour la prescription et la mise en œuvre des programmes d'activité physique adaptée (APA) pour soutenir le RAT chez les survivantes du cancer du sein.

Trois études présentées sous forme d'articles de recherche ont été réalisées pour répondre à ces objectifs.

2. Méthodologie

Pour répondre aux questions de recherche de la thèse, nous avons utilisé la méthodologie basée sur la synthèse des preuves. La synthèse des preuves se réfère au processus et méthodes de

compilation des preuves générées par les études primaires, qu'elles soient qualitatives, quantitatives ou une combinaison des deux, afin de répondre à des questions de recherche ou de prendre des décisions (Langlois et al., 2018 ; Royal Society, 2018). Selon Cochrane, la synthèse des données probantes "consiste à combiner les données de plusieurs études portant sur le même sujet afin de bien comprendre leurs résultats et d'établir des preuves pour les meilleures pratiques" (Cochrane, 2019). En intégrant les résultats et les données de nombreuses études empiriques, la synthèse des données probantes répond à une question de recherche avec une forte puissance (Gough et al., 2020 ; Snyder, 2019). Ainsi, elle aide les décideurs politiques, les établissements de santé, les cliniciens, les chercheurs et le public à prendre des décisions plus éclairées en ce qui concerne la santé et les soins de santé (Cochrane, 2019).

Dans le cadre de cette thèse, nous avons utilisé les méthodes de revue systématique et de méta-analyse, ainsi que la revue rapide pour répondre aux deux premières questions de recherche (objectif 1 et 2).

Enfin, pour répondre à l'objectif 3, nous avons utilisé une méthode de consensus basée sur l'expertise d'un professionnel d'APA ayant des expériences sur la prise en charge des personnes atteintes d'un cancer. Plus précisément, les résultats des deux premières études ont été utilisés pour proposer une première version de protocoles, qui a été soumise pour discussion avec un professionnel d'APA. Une version finale des protocoles a été proposée et validée après consensus.

3. Principaux résultats

La première partie de la thèse a évalué l'efficacité des interventions d'AP sur le RAT chez les survivants du cancer et déterminer la dose d'AP nécessaire pour améliorer le RAT. La synthèse narrative a montré que les interventions d'AP supervisées, comprenant des exercices aérobique et de résistance, effectuées pendant et/ou après le traitement du cancer, améliorent le RAT chez les survivants du cancer. La méta-analyse a montré un risque relatif (RR) global de 1,29 (IC à 95 % : 1,17, 1,42) chez les survivants du cancer qui ont bénéficié des interventions d'AP. Ces résultats révèlent que les interventions d'AP ont un effet positif significatif sur le RAT après un diagnostic de cancer, par rapport aux soins habituels. En outre, la méta-régression a mis en évidence une relation linéaire positive entre la dose d'AP et le RAT. Ainsi, nous avons déterminé qu'une dose d'AP

comprise entre 7,6 METs-h/semaine et 15 METs-h/semaine semble appropriée pour améliorer le RAT chez les survivants du cancer. Cela correspond à 100-120 minutes par semaine d'exercice modéré à vigoureux, réparties deux fois par semaine. Dans l'ensemble, les résultats de la première étude montrent avec des preuves modérées que les interventions d'AP sont plus efficaces que les soins habituels pour améliorer le RAT chez les survivants du cancer.

Concernant l'étude 2, nous avons identifié neuf directives recommandant l'AP pour les survivants du cancer et élaborées dans les pays développés, dont la France. Cinq directives sont de bonne qualité et recommandées pour la pratique clinique. Cependant, la directive élaborée en France par la Haute Autorité de Santé (HAS) n'a pas été retenue parmi les cinq à cause de sa faible qualité méthodologique, soulevant la question de son utilisation en pratique clinique. L'étude a également permis de mettre en évidence que l'AP est sans risque, faisable et bien tolérée chez les survivants du cancer. L'AP peut être prescrite et pratiquée à toute les phases de la maladie (c'est-à-dire avant, pendant et/ou après le traitement du cancer). Par ailleurs, toutes les directives recommandent de prévenir l'inactivité après un diagnostic de cancer. Elles préconisent que l'AP soit adaptée aux préférences, aux préférences et aux capacités physiques des patients atteints de cancer. Les bénéfices l'AP chez les patients sont plus importants si elle est pratiquée sous la supervision d'un professionnel d'APA. Ces recommandations sont applicables pour atténuer les symptômes physiques et psychologiques liés au cancer et ses traitements. Cependant, les directives actuelles ne sont pas applicables pour améliore le RAT des survivants du cancer. Ces résultats suggèrent la nécessité d'élaborer de nouvelles directives pour soutenir le RAT des patients atteints de cancer, spécifiquement les survivantes du cancer du sein.

C'est à ce besoin que répond l'étude 3 qui a pour objectif de proposer un guide avec des protocoles pratiques pour prescrire et mettre en œuvre un programme d'activité physique adaptée (APA) pour soutenir le RAT chez les survivantes du cancer du sein.

L'étude 3 est basée sur la combinaison des résultats des études 1 et 2 (résultats fondés sur des données probantes) et sur l'expertise d'un professionnel d'APA ayant des expériences sur la prise en charge des personnes atteintes d'un cancer. Les discussions avec l'expert ont abouti à un

consensus pour proposer des protocoles en fonction des trois principales phases du continuum de traitement du cancer (pré-habilitation, pendant et après). Ainsi, nous avons proposé ;

100 à 120 minutes par semaine d'exercices aérobiques et de résistance d'intensité modérée à vigoureuse (au moins 4,5 MET).

L'exercice doit être réparti sur 2 à 3 fois par semaine pendant au moins 12 à 20 semaines.

Avant de commencer les programmes d'AP, il est nécessaire d'effectuer des évaluations médicales et de pré-exercice. L'AP doit être initiée dès que possible après le diagnostic du cancer, sous la supervision d'un professionnel de l'exercice physique, et en milieu hospitalier.

Des exemples pratiques de prescription et de mise en œuvre des programmes d'AP ont également été fournis.

4. Conclusion et perspectives

Les résultats de la thèse ont montré que l'AP est plus efficace pour améliorer le RAT des survivants du cancer comparé aux soins habituels. La thèse a également contribué à déterminer la dose d'AP nécessaire pour améliorer le RAT après un cancer. En résumé, cette thèse a démontré avec des preuves modérées l'efficacité de l'AP sur le RAT chez les survivants du cancer. Il s'agit d'une preuve supplémentaire des effets bénéfiques de l'AP chez les patients atteints de cancer.

De plus, les recommandations des directives d'AP pour les survivants du cancer montrent que l'AP est sans risque et peut être pratiquée à toutes les phases de la maladie conformément aux recommandations. Néanmoins, ces recommandations ne sont pas applicables pour améliorer le RAT des patients atteints de cancer. Cependant, nous avons proposé un guide avec des protocoles pratiques pour aider les professionnels de santé et les professionnels d'APA à prescrire et à mettre en œuvre des programmes d'AP pour soutenir le RAT chez les survivants du cancer. Nous n'avons pas pu évaluer l'applicabilité et l'utilisation de ces protocoles en pratique clinique. Des recherches futures sont donc nécessaires pour évaluer l'applicabilité des protocoles proposés.

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APPENDICES AND ANNEXES

1. APPENDICE 1. SUPPLEMENTARY TABLES OF STUDY 1

Effectiveness of physical activity interventions on return to work after a cancer diagnosis: a systematic review and meta-analysis.

Têtê Norbert Wilson[1]*, Aboubakari Nambiema[1], Bertrand Porro[1], Alexis Descatha[1], Agnès Aublet-Cuvelier[2], Bradley Evanoff[3], Yves Roquelaure[1]

Affiliations

[1]Univ Angers, CHU Angers, Univ Rennes, Inserm, EHESP, Irset (Institut de recherche en santé, environnement et travail)-UMR_S 1085, F-49000 Angers, France

[2]INRS (Institut National de Recherche et de Sécurité), Direction des Etudes et de Recherches, 1 rue du Morvan, CS60027, 54519 Vandœuvre-lès-Nancy, France

[3]Division of General Medical Sciences, Washington University School of Medicine, St. Louis, MO 63310, USA, Saint-Louis, USA

***Corresponding author:** Têtê Norbert Wilson (Ph.D .Student), tetenorbert.wilson@etud.univ-angers.fr

ORCID ID: https://orcid.org/0000-0003-1696-7454

SUPPLEMENTARY MATERIALS OS STUDY 1

Table A Search strategies and results.

Database	Search string	Record Count 08/12/2020	Upgrade 30/09/2021
PubMed	(exercise[MH] OR running[TW] OR gymnastics[TW] OR “aerobic exercise”[TW] OR “exercise therapy”[MH] OR “exercise program*”[TW] OR “sports”[MH] OR sports[TW] OR “physical activit*”[TW] OR “physical training”[TW] OR “physical exercise”[TW] OR “physical fitness”[TW] OR “breathing exercise*”[TW] OR “stretching exercise*”[TW] OR “remedial exercise*”[TW] OR (“exercise”[TW] AND “rehabilitation”[TW])) AND (“return to work”[MH] OR “back-to-work”[TW] OR “return to work”[TW] OR "work resumption"[TW] OR "work rehabilitation"[TW] OR "work reintegration"[TW] OR "work retention"[TW] OR reemployment[TW] OR “occupational medicine”[MH] OR “occupational health”[MH] OR “occupational therapy”[TW] OR “occupational medicine”[TW] OR “occupational health”[TW] OR employee[TW] OR “sick leave”[MH] OR absenteeism[MH] OR ((resume[TW] OR re-enter[TW] OR re-entry[TW]) AND (job[TW] OR work[TW] OR labour[TW]))) AND (neoplasms[MH] OR cancer*[TW] OR tumo*[TW] OR carcinoma[TW] OR lymphoma[TW] OR leukemia[TW] OR melanoma[TW] OR sarcoma[TW] OR blastoma[TW] OR oncolog*[TW])	191	**210**
Embase	('exercise'/exp OR 'running'/exp OR gymnastics:ti,ab,kw OR 'aerobic exercise':ti,ab,kw OR 'exercise therapy':ti,ab,kw OR 'exercise program*':ti,ab,kw OR sport*:ti,ab,kw OR 'physical activit*':ti,ab,kw OR 'physical training':ti,ab,kw OR 'physical exercise':ti,ab,kw OR 'physical fitness'/exp OR 'breathing exercise*':ti,ab,kw OR 'stretching exercise*':ti,ab,kw OR 'remedial exercise*':ti,ab,kw OR (execise:ti,ab,kw AND 'rehabilitation'/exp)) AND ('return to work'/exp OR 'back-to-work':ti,ab,kw OR 'work resumption':ti,ab,kw OR 'work rehabilitation':ti,ab,kw OR 'work reintegration':ti,ab,kw OR 'work retention':ti,ab,kw OR reemployment:ti,ab,kw OR 'occupational medicine':ti,ab,kw OR 'occupational health':ti,ab,kw OR 'occupational therapy':ti,ab,kw OR employee:ti,ab,kw OR 'sick leave':ti,ab,kw OR 'absenteeism'/exp OR ((resume:ti,ab,kw OR 're-enter':ti,ab,kw OR 're-entry':ti,ab,kw) AND (job:ti,ab,kw OR work:ti,ab,kw OR labour:ti,ab,kw))) AND ('neoplasm'/exp OR cancer*:ti,ab,kw OR tumo*:ti,ab,kw OR carcinoma:ti,ab,kw OR lymphoma:ti,ab,kw OR leukemia:ti,ab,kw OR melanoma:ti,ab,kw OR sarcoma:ti,ab,kw OR blastoma:ti,ab,kw OR oncolog*:ti,ab,kw)	278	**314**
Cochrane Library	1. ((exercise):ti,ab,kw OR (running):ti,ab,kw OR (gymnastics):ti,ab,kw OR (aerobic exercise):ti,ab,kw OR “exercise program*”:ti,ab,kw OR ("exercise therapy"):ti,ab,kw OR (sport*):ti,ab,kw OR ("physical activit*"):ti,ab,kw OR ("physical training"):ti,ab,kw OR ("physical exercise"):ti,ab,kw OR ("physical fitness"):ti,ab,kw OR ("breathing exercise*"):ti,ab,kw OR ("stretching exercise*"):ti,ab,kw OR ("remedial exercise*"):ti,ab,kw OR (exercise:ti,ab,kw AND rehabilitation:ti,ab,kw)) 2. ("return to work"):ti,ab,kw OR (“back-to-work”):ti,ab,kw OR (work resumption):ti,ab,kw OR (work rehabilitation):ti,ab,kw OR (work reintegration):ti,ab,kw OR (work retention):ti,ab,kw OR (reemployment):ti,ab,kw OR ("occupational medicine"):ti,ab,kw OR	174	**188**

	("occupational health"):ti,ab,kw OR ("occupational therapy"):ti,ab,kw OR (employee):ti,ab,kw OR ("sick leave"):ti,ab,kw OR (absenteeism):ti,ab,kw 3. (resume:ti,ab,kw OR re-enter:ti,ab,kw OR re-entry:ti,ab,kw) AND (job:ti,ab,kw OR work:ti,ab,kw OR labour:ti,ab,kw) **4. (#2 OR #3)** #5. (neoplasms:ti,ab,kw OR cancer*:ti,ab,kw OR tumo*:ti,ab,kw OR carcinoma:ti,ab,kw OR lymphoma:ti,ab,kw OR leukemia:ti,ab,kw OR melanoma:ti,ab,kw OR sarcoma:ti,ab,kw OR blastoma:ti,ab,kw OR oncolog*:ti,ab,kw) **6. (#1 AND #4 AND #5)**		
Web of Sciences	TS=((exercise OR running OR gymnastics OR "aerobic exercise" OR "exercise therapy" OR "exercise program*" OR sport* OR "physical activit*" OR "physical training" OR "physical exercise" OR "physical fitness" OR "breathing exercise*" OR "stretching exercise*" OR "remedial exercise*" OR ("exercise" AND "rehabilitation")) AND ("return to work" OR "back-to-work" OR "work resumption" OR "work rehabilitation" OR "work reintegration" OR "work retention" OR reemployment OR "occupational medicine" OR "occupational health" OR "occupational therapy" OR employee OR "sick leave" OR absenteeism OR ((resume OR re-enter OR re-entry) AND (job OR work OR labour))) AND (neoplasms OR cancer* OR tumo* OR carcinoma OR lymphoma OR leukemia OR melanoma OR sarcoma OR blastoma OR oncolog*))	344	**375**
Scopus	TITLE-ABS-KEY((exercise OR running OR gymnastics OR "aerobic exercise" OR "exercise therapy" OR"exercise program*" OR sport* OR "physical activit*" OR "physical training" OR "physical exercise" OR "physical fitness" OR "breathing exercise*" OR "stretching exercise*" OR "remedial exercise*" OR (exercise AND rehabilitation)) AND ("return to work" OR "back-to-work" OR "work resumption" OR "work rehabilitation" OR "work reintegration" OR "work retention" OR reemployment OR "occupational medicine" OR "occupational health" OR "occupational therapy" OR employee OR "sick leave" OR absenteeism OR ((resume OR re-enter OR re-entry) AND (job OR work OR labour))) AND (neoplasms OR cancer* OR tumo* OR carcinoma OR lymphoma OR leukemia OR melanoma OR sarcoma OR blastoma OR oncolog*))	686	**745**
Psycinfo	(DE(exercise OR sports) OR TX(running OR gymnastics OR "aerobic exercise" OR "exercise therapy" OR "exercise program*" OR sports OR "physical activit*" OR "physical training" OR "physical exercise" OR "physical fitness" OR "breathing exercise*" OR "stretching exercise*" OR "remedial exercise*" OR ("exercise" AND "rehabilitation"))) AND (DE ("occupational therapy" OR "occupational health") OR TX("return to work" OR "back-to-work" OR "work resumption" OR "work rehabilitation" OR "work reintegration" OR "work retention" OR reemployment OR "occupational medicine" OR "occupational health" OR "occupational therapy" OR employee OR "sick leave" OR absenteeism OR ((resume OR re-enter OR re-entry) AND (job OR work OR labour)))) AND (DE(neoplasms) OR TX(cancer* OR tumo* OR carcinoma OR lymphoma OR leukemia OR melanoma OR sarcoma OR blastoma OR oncolog*))	145	**151**

Clinical Trials Gov	(exercise OR running OR gymnastics OR “aerobic exercise” OR “exercise therapy” OR sport* OR “physical activit*” OR “physical training” OR “physical exercise” OR “physical fitness” OR “breathing exercise*” OR “stretching exercise*” OR “remedial exercise*” OR “exercise” AND “rehabilitation”) AND (“return to work” OR “back-to-work” OR “work resumption” OR “work rehabilitation” OR “work reintegration” OR “work retention” OR reemployment OR “occupational medicine” OR “occupational health” OR “occupational therapy” employee OR “sick leave” OR absenteeism OR (resume OR re-enter OR re-entry) AND (job OR work OR labour)) AND (neoplasms OR cancer* OR tumo* OR carcinoma OR lymphoma OR leukemia OR melanoma OR sarcoma OR blastoma OR oncolog*) AND AREA[OverallStatus] EXPAND[Term] COVER[FullMatch] ("Recruiting" OR "Active, not recruiting" OR "Completed" OR "Enrolling by invitation" OR "Terminated" OR "Unknown status")	178	**203**
Google Scholar	(“physical activity” OR “physical training” OR “physical fitness” OR (“exercise” AND “rehabilitation”)) AND (“return to work” OR “back-to-work” OR "work retention" OR reemployment) AND (cancer OR neoplasms) / sort by relevance AND exclude patents.	200	**200**
Opengrey	("return to work")	28	**43**
Osha	("physical activity" OR exercise) AND (cancer OR neoplasms) AND ("return to work" OR "back-to-work" OR rehabilitation) / filter on type of publication.	45	**78**
Inca	("physical activity" OR exercise) AND (cancer OR neoplasms OR tumor) AND ("return to work" OR back-to-work OR rehabilitation)	82	**88**
American Society of Clinical Oncology (ASCO)	return to work/ filter on Abstracts/	46	**52**

Table B Typology and definition of physical activities components in interventions.

Types of Physical Activity	Definition	Example
Physical activity (PA)	is defined as any bodily movement produced by skeletal muscles that result in energy expenditure, which can be measured in kilocalories (as energy expenditure).	Exercise, sport, PA done as part of daily living, occupation, leisure, and active transportation.
Exercise	Exercise is a form of physical activity that is planned, structured, repeated and has a final or an intermediate objective to the improve or maintain physical fitness and health.	According to PA guideline for Americans[c], exercises have been classified in four main types: aerobic exercise, resistance exercise, flexibility exercise and balance.
Aerobic or endurance exercise	also called endurance exercise, it is any physical activity that uses large muscle groups and causes your body to use more oxygen than it would while resting. It causes a person's heart to beat faster, and they will breathe harder than normal. It is the type of movement that most benefits the heart.	*Examples* of aerobic activity are running, swimming, dancing, brisk walking, jogging, and bicycling.
Resistance or strength exercise	also called strength training (muscles and bone strengthening), it can firm, strengthen, and tone your muscles, as well as improve bone strength, balance, and coordination.	*Examples:* exercises, bicep curls, shoulder press, bench press, barbell squat, pushups, lunges, pelvic floor muscle training, and bent over row.
Flexibility or stretching exercises	Flexibility exercises stretch your muscles and can help your body stay flexible. These activities help to improve joint flexibility and keep muscles limber, thereby preventing injury.	*Example:* yoga and Pilates
Balance activity	These kinds of exercise can improve the ability to resist forces within or outside of the body that cause falls while a person is stationary or moving.	*Example:* Walking backward, standing on one leg.

[c] The Physical Activity Guidelines for Americans were published by the United States department of health and human services. It provides information and guidance on the types and amounts of physical activity to improve a variety of health outcomes for multiple population groups.

Table C Details of risk of bias assessment for each included study.

Study ID	Bias	Domains	Judgements	Comments
1. Mijwel et al, 2019	*Selection bias*	Study group	**LOW**	Participants were randomly allocated to RT-HIIT, AT-HIIT, or UC using a random assignment computer program at a 1:1:1 ratio as per original paper (*Mijwel et al, 2018*). At 12 months, 95% of the women who completed pre- and post-measurements filled out all questionnaires and 78% agreed to come back for in-clinic physiological reassessments.
	Performance bias	Blinding	PROBABLY LOW	Impossible to blind participants due to the nature of the intervention. The assignment program was blinded to the research team, prior to the first assessment. Exercise supervisors weas not masked to group allocation. The outcome was self- assessed by participants using self-reported questionnaires. According to the study design the lack of blinding did not affect outcome measure (assessed by standard metrics tool).
	Detection bias	Intervention assessment	PROBABLY LOW	There is insufficient information about intervention assessment. However, the study design (RCT) allows for accurate assessment. PA intervention was performed **according to standardized protocol followed by each participant.**
		Outcome assessment	PROBABLY LOW	The outcome (return to work) was self-reported using questionnaire (regarding how much sick leave the participants were taking at 12 months) **that is suggest being robust methods.**
	Confounding bias	Confounding	PROBABLY LOW	The study did not account the confounders for secondary outcome analysis. However, **the randomization minimizes confounders, and this is not expected to introduce substantial bias**.
	Attrition bias	Incomplete Outcome Data	PROBABLY HIGH	The missing data (32/173 = 18%) were showed in flow chat but not described in the data analysis. Small dropouts (loss to follow-up limited) and high response rate.
	Reporting bias	Selective outcome reporting	PROBABLY LOW	There is no evidence of selective reporting. Based on the outcomes outlined in the published manuscript's methods, all outcomes have been reported in the pre- specified way. The study was free of selective reporting.
	Conflict of interest	Conflict of interests	**LOW**	No conflict of interest detected. The study was supported by the Swedish

				foundations, academy grants and by government.
	Other risk of bias	Other Bias	PROBABLY HIGH	Data were not analyzed by ITT.
2. Jong et al (2018)	*Selection bias*	Study group	PROBABLY LOW	Participants were randomized using separate randomization lists (using blocked randomization) and assigned to four strata. Lack of information concerning the recruitment and enrollment procedures. In addition, the recruitment remained at a lower than anticipated rate and the participation rate was approximately **35%** (83/239) of eligible participants.
	Performance bias	Blinding	PROBABLY LOW	Impossible to blind participants due to the nature of the intervention. The study monitor was blinded for allocation sequence and assigned subjects to the groups. The outcome was self- assessed by participants using semi-structured telephone interview. **According to the study design the lack of blinding did not affect outcome measure (assessed by standard metrics tool).**
	Detection bias	Intervention assessment	PROBABLY LOW	There is insufficient information about intervention assessment. However, the study design (RCT) allows for accurate assessment. PA intervention was performed according **to standardized protocol followed by each participant**.
		Outcome assessment	PROBABLY LOW	The outcome (return to work) was assessed by self-reported using semi-structured telephone interview carried out by the research physician at 3 and at 6 months follow-up. **That is suggest being robust methods.**
	Confounding bias	Confounding	PROBABLY LOW	The study did not account the confounders for outcomes analysis. However, the randomization and stratification minimize confounders, **and this is not expected to introduce substantial bias.**
	Attrition bias	Incomplete Outcome Data	PROBABLY HIGH	Not all participants who were randomized were accounted for at 3 months. General missing data were reported in the flowchart, but no precision concerning those with the outcome and not imputed in analysis.
	Reporting bias	Selective outcome reporting	PROBABLY LOW	No protocol published. Based on the outcomes outlined in the published manuscript's methods, all outcomes have been reported in the pre- specified way. There is no evidence of selective reporting.
	Conflict of interest	Conflict of interests	**LOW**	No competing financial interests exist. The study was funded by a public

				founding (Pink Ribbon (Grant: 2011, W016.C97).
	Other risk of bias	Other Bias	PROBABLY LOW	More participants were randomized to the intervention group than to control group. This resulted in an imbalance of participants between the two groups. The large difference in group size probably explained the finding that the two comparison groups differed at baseline for several primary and secondary outcome parameters.
3. Ibrahim et al (2017)	*Selection bias*	Study group	**LOW**	Participants (a total of 59 young women) were equally randomized into the control (n= 30) and intervention (n= 29) arm. A block randomization process was used to generate a table through hhttp://www.randomization.com. There is sufficient information about inclusion/exclusion criteria. No statistically significant differences were observed among the intervention and control arm's baseline characteristics.
	Performance bias	Blinding	PROBABLY LOW	Impossible to blind participants due to the nature of the intervention. However, access to the randomization table was limited to a single individual, and the treatment assignment was hidden until a participant's name was entered. Participants were the outcome assessors (as using self-reported post hoc questionnaire). **According to the study design that the lack of blinding did not affect outcome measure (assessed by standard metrics tool).**
	Detection bias	Intervention assessment	PROBABLY LOW	There is insufficient information about intervention assessment. However, the study design (RCT) allows for accurate assessment. PA intervention was performed according **to standardized protocol followed by each participant**.
		Outcome assessment	PROBABLY LOW	The outcome (return-to-work) was assessed using a post hoc questionnaire to compare participants' pre-diagnostic work hours.
	Confounding bias	Confounding	PROBABLY LOW	The study did not account the confounders for outcomes analysis. However, the randomization minimizes confounders, and this is not expected to introduce substantial bias.
	Attrition bias	Incomplete Outcome Data	PROBABLY HIGH	Two dropped out and 3 died during the study. At 18 months follow-up, 8 patients **(13.56%)** have missing data because of several document events. Missing data were not included in the analysis.

	Reporting bias	Selective outcome reporting	PROBABLY LOW	No protocol published. Based on the outcomes outlined in the published manuscript's methods, all outcomes have been reported in the pre- specified way. There is no evidence of selective reporting.
	Conflict of interest	Conflict of interests	**LOW**	Funding source is from non-profit organization and government agencies. Authors declare no conflict of interest.
	Other risk of bias	Other Bias	PROBABLY HIGH	The low adherence to the use of self-reported logs. Moreover, intention-to-treat analysis was not performed.
4. Van Waart et al (2015)	*Selection bias*	Study group	PROBABLY LOW	Patients were randomly assigned to Onco-Move, OnTrack, or UC groups using the minimization method for allocation to clinical trials. **There is insufficient information concerning the recruitment and enrollment procedures (inclusion/exclusion criteria).** No significant difference in background characteristics between participants and non-participants. Participation rate **44%** (230 of 524 eligible patients).
	Performance bias	Blinding	PROBABLY LOW	Impossible to blind participants due to the nature of the intervention. Lack of information about blinding of study investigators. Participants were the outcome assessors (as using self-reported RTW questionnaire). **According to the study design, absence of blinding judged as not significantly impacting outcome measure (assessed by standard metrics tool).**
	Detection bias	Intervention assessment	PORBABLY LOW	There is insufficient information about intervention assessment. However, the study design (RCT) allows for accurate assessment. PA intervention was performed according **to standardized protocol followed by each participant**.
		Outcome assessment	PROPABLY LOW	The outcome (return to work) was self-reported. Patients underwent performance-based tests and completed questionnaires at completion of chemotherapy (T1), and 6 months after completion of chemotherapy (T2).
	Confounding bias	Confounding	PROPABLY LOW	The inclusion (randomization) minimizes the confounders and did not affect the result.
	Attrition bias	Incomplete Outcome Data	PROBABLY LOW	All analyses were conducted on an intention-to-treat basis. However, outcome data were available for 204 participants (89%) directly after chemotherapy, and for 196 (85%) at the 6-month follow-up. Missing data not imputed.

	Reporting bias	Selective outcome reporting	PROBABLY LOW	No protocol published. Based on the outcomes outlined in the published manuscript's methods, all outcomes have been reported in the pre- specified way. There is no evidence of selective reporting.
	Conflict of interest	Conflict of interests	PROBABLY HIGH	The study was supported by public agencies. However, two authors declared research funding from pharmaceutical Labs (Novartis Roche and AstraZeneca).
	Other risk of bias	Other Bias	PROBABLY LOW	All analyses were conducted on an intention-to-treat basis. Half of the eligible patients declined to participate in the trial. This is a common finding in exercise oncology trials and raises issues regarding the generalizability of results to the larger target population.
5. Thijs et al (2012)	*Selection bias*	Study group	PROBABLY HIGH	Patients were not randomized. There is sufficient information about the recruitment and enrollment procedures (inclusion/exclusion criteria). The response rate was 95 % in the intervention group and 74% in the control group. There is no significant differences in patient characteristics at baseline between the two groups.
	Performance bias	Blinding	PROBABLY HIGH	Impossible to blind participants due to the nature of the intervention. No blinding, the outcome was reported by the patients (self-reported) with validated telephonic job resumption questionnaire.
	Detection bias	Intervention assessment	PROBABLY LOW	There is insufficient information about intervention assessment. However, the study design allows for accurate assessment. PA intervention was performed by each participant follow **standardized methods and supervised**.
		Outcome assessment	PROBABLY LOW	The outcome (return-to-work) was assessed using a telephonic job resumption questionnaire validated in research on chronic diseases and work **that is suggest being robust methods.**
	Confounding bias	Confounding	PROBABLY LOW	The design of the study allows to minimize the confounders (**age matched controlled**). In addition, analyses were adjusted to most important confounders (age, sex, education level), but other confounders may also be relevant.
	Attrition bias	Incomplete outcome data	PROBABLY LOW	No missing data for outcome reported and no loss of follow-up. However, **11 patients in control group were excluded from the main analysis.**
	Reporting bias	Selective outcome reporting	PROBABLY LOW	No protocol published. Based on the outcomes outlined in the published manuscript's methods, all outcomes have been reported in the pre- specified

				way. There is no evidence of selective reporting.
	Conflict of interest	Conflict of interests	**LOW**	The study was financed by non-profit organizations. No commercial party having a direct financial interest in the study results.
	Other risk of bias	Other Bias	PROBABLY HIGH	Difficult to generalize results to patients with other cancer because of high number breast cancer patients. Patients were not able to exactly recall the details and times of return-to-work can introduce memory bias.
6. Burgio et al (2006)	*Selection bias*	Study group	**LOW**	Participants were randomized using computer generated random numbers and a block size of 4. Participant's selection, inclusion and exclusion criteria were described. No significant differences were found between the groups on key variables.
	Performance bias	Blinding	PROBABLY LOW	Impossible to blind participants due to the nature of the intervention. The randomization schedule was implemented by the research nurse, so that interventionists would be blinded to the next group assignment. Participants were the outcome assessors (as using self-reported RTW questionnaire). **According to the study design, absence of blinding judged as not significantly impacting outcome measure (assessed by standard metrics tool).**
	Detection bias	Intervention assessment	PROBABLY LOW	The study design (RCT) allows for accurate intervention assessment. PA intervention was performed by each participant following standardized methods described in the study.
		Outcome assessment	PROBABLY LOW	The outcome (return-to-work) was self-assessed 6 weeks, 3 months and 6 months following surgery reported using a standard questionnaire that is suggest being robust methods.
	Confounding bias	Confounding	PROBABLY LOW	Analysis did not take into account confounders. However, prior to randomization, patients were stratified by age, tumor differentiation. In addition, the study design RCT allows to minimize the confounding bias.
	Attrition bias	Incomplete Outcome Data	PROBABLY LOW	No information was provided for patients with missing data. **The drop-out were not important (lower rate) in groups and reasons for drop-out are given.**
	Reporting bias	Selective outcome	PROBABLY LOW	No protocol published. Based on the outcomes outlined in the published

		reporting		manuscript's methods, all outcomes have been reported in the pre- specified way.
	Conflict of interest	Conflicts of interest	**LOW**	The study was supported by grant from public agencies.
	Other risk of bias	Other Bias	PROBABLY HIGH	**An intent-to-treat analysis did not perform**. For the work-related data for people working at baseline no attrition/exclusion statistics were given.
7. Rogers et al (2009)	*Selection bias*	Study group	**LOW**	Participants were randomized after completion of all baseline assessments. Randomization was computer generated and kept in sealed envelopes until randomization to prevent bias in group allocation by study personnel. Recruitment process was described, eligibility criteria (inclusion/exclusion) were reported. No significant differences in patient characteristics at baseline between the two groups.
	Performance bias	Blinding	PROBABLY LOW	Impossible to blind participants due to the nature of the intervention. The randomization was implemented to prevent bias in group allocation by study personnel. Participants were the outcome assessors (as using self-reported RTW questionnaire). **According to the study design, absence of blinding judged as not significantly impacting outcome measure (assessed by standard metrics tool).**
	Detection bias	Intervention assessment	PROBABLY LOW	There is insufficient information about intervention assessment. However, the study design allows for accurate assessment, PA intervention was performed by each participant follow standardized methods **according to specific protocol**.
		Outcome assessment	PROBABLY LOW	The outcome was self-reported (using standard self-reported questionnaires) that is suggest being robust methods. Measurement was obtained after 3 months (immediately post-intervention).
	Confounding bias	Confounding	PROBABLY LOW	Analysis did not take into account confounders. In addition, the study design RCT allows to minimize the confounding bias.
	Attrition bias	Incomplete Outcome Data	PROBABLY LOW	The authors provide an assessment of missing data in the statistical analysis section (for individual items on scales and imputation) and for those lost to follow-up. Attrition after randomized was 7% (3/41). Reasons for drop-out are

				reported. However, the numbers on each outcome are not provided in the tables so assumed all others were complete or imputed.
	Reporting bias	Selective outcome reporting	PROBABLY LOW	No selective report suspected. All outcomes from methods were reported.
	Conflict of interest	Conflict of interests	**LOW**	The project was supported by public academic grants and foundation. The authors did not have any relationships to disclose that would cause a conflict of interest.
	Other risk of bias	Other Bias	**LOW**	No other source of bias was identified. **ITT analysis was performed**.
8. Berglund et al (1994)	*Selection bias*	Study group	PROBABLY LOW	Patients who accepted were randomized to the intervention group or to the control group. Efron's method for randomization of small samples was used. Inclusion criteria were described. Participation's response rate and reasons for non-responses were provided. 73 other patients declined participation but agreed to complete the questionnaire (**73/272 = 26.8 %**). There were no differences between the intervention and the control groups at any time assessed.
	Performance bias	Blinding	PROBABLY LOW	Impossible to blind participants due to the nature of the intervention. Participants were the outcome assessors. There is not information about investigator blinding. **According to the study design, absence of blinding judged as not significantly impacting outcome measure (assessed by standard metrics tool).**
	Detection bias	Intervention assessment	PROBABLY LOW	There is insufficient information about intervention assessment. However, the study design allows for accurate assessment, PA intervention was performed by each participant follow standardized methods **according to specific protocol**.
		Outcome assessment	PROBABLY LOW	The Outcome (sick leave) was self-assessed (using standard self-reported questionnaires) that is suggest being robust methods. Measurement was obtained at 3, 6 and 12 months (post-intervention).
	Confounding bias	Confounding	PROBABLY LOW	Analysis did not allow to consider confounders. However, the study design RCT allows to minimize the confounding bias.

	Attrition bias	Incomplete Outcome Data	PROBABLY LOW	No missing data for outcome reported and loss to follow-up not important/ no different.
	Reporting bias	Selective outcome reporting	PROBABLY LOW	No selective report suspected. All outcomes from study methods are reported.
	Conflict of interest	Conflict of interests	**LOW**	The study is supported by a grant from the Swedish foundation.
	Other risk of bias	Other Bias	PROBABLY HIGH	ITT analysis was not performed. ANOVA scores are based on those patients who provided data for all points of assessment.

Table D PRISMA 2009 Checklist

Section/topic	Items #	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5-6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6 and supplementary Table A
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6

Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8

Section/topic	Items #	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8-9 and Fig. 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9-10 and Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	10-11
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	11
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	11
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	11

Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	12-13
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	13-15
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	15-16
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16-17
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	1

2. APPENDICE 2. SUPPLEMENTARY TABLES OF STUDY 2

Physical activity in people diagnosed with cancer: A rapid review of recommendations and critical appraisal of international guidelines.

Têtê Norbert Wilson[1], Yves Roquelaure[1,2], Bradley Evanoff[3], Agnès Aublet-Cuvelier[4], Bertrand Porro[1,5]

[1]Univ Angers, Univ Rennes, Inserm, EHESP, Irset (Institut de recherche en santé, environnement et travail) - UMR_S 1085, IRSET-ESTER, SFR ICAT, F-49000 Angers, France

[2]Univ Angers, CHU Angers, Univ Rennes, Inserm, EHESP, Irset (Institut de recherche en santé, environnement et travail) - UMR_S 1085, IRSET-ESTER, SFR ICAT, F-49000 Angers, France

[3]Division of General Medical Sciences, Washington University School of Medicine, MO 63310, Saint Louis, USA.

[4]INRS (Institut National de Recherche et de Sécurité), Direction des Etudes et de la Recherche, 1 rue du Morvan, CS60027, 54519 Vandœuvre-lès-Nancy, France

[5]Department of Human and Social Sciences, Institut de Cancérologie de l'Ouest (ICO), 49055 Angers, France

Corresponding Author: Têtê Norbert Wilson, University of Angers, Faculty of Health, Ester Laboratory, 28 rue Roger Amsler, CS 74521 49045 ANGERS Cedex 01, tetenorbert.wilson@etud.univ-angers.fr

ORCID ID: https://orcid.org/0000-0003-1696-7454

SUPPLEMENTARY TABLES STUDY 2

Table S1. Search strategies and results.

Databases	Search queries	Results
	Indexed databases	
MEDELINE/PubMed	("physical activity"[Title/Abstract] OR "exercise"[MeSH Terms] OR "physical exercise"[Title/Abstract]) AND ("cancer"[Title/Abstract] OR "neoplasms"[MeSH Terms] OR "cancer patients"[Title/Abstract] OR "cancer survivors"[Title/Abstract]) AND ("Consensus"[MESH] OR "Consensus development conferences as topic"[MESH] OR "Guidelines as topic" OR "Practice guidelines as topic"[MESH] OR "Health planning guidelines"[MESH] OR "Clinical Decision Rules"[MESH] OR "guideline"[pt] OR "practice guideline"[pt] OR "consensus development conference"[pt] OR "consensus development conference, NIH"[pt] OR position statement*[tiab] OR policy statement*[tiab] OR practice parameter*[tiab] OR best practice*[tiab] OR standards[TI] OR guideline[TI] OR guidelines[TI] OR standards[ot] OR guideline[ot] OR guidelines[ot] OR guideline*[cn] OR standards[cn] OR consensus*[cn] OR recommendat*[cn] OR practice guideline*[tiab] OR treatment guideline*[tiab] OR CPG[tiab] OR CPGs[tiab] OR clinical guideline*[tiab] OR guideline recommendation*[tiab] OR consensus*[tiab])	587
EMBASE	('physical activity':ti,ab,kw OR 'exercise'/exp OR 'physical exercise':ti,ab,kw) AND (cancer:ti,ab,kw OR neoplasms:ti,ab,kw OR 'cancer patients':ti,ab,kw OR 'cancer survivors':ti,ab,kw) AND ((guidelines:ti,ab,kw OR 'guideline'/exp OR recommendat*:ti,ab,kw OR 'position statement*':ti,ab,kw) AND ('evidence based medicine'/de OR 'practice guideline'/de))	962
Google Scholar	(“physical activity” OR exercise OR “physical exercise”) AND (cancer OR neoplasms OR “cancer patients” OR “cancer survivors”) AND (guidelines OR recommendations) / sort by relevance AND Journal articles	200
	Cancer organization websites and guidelines databases	
Cancer organizations Websites (ACS, INCa, CCS, BCRI)	(“physical activity” OR exercise OR “physical exercise”) AND (“cancer patients” OR “cancer survivors”) AND (guidelines OR recommendations)	50
GuidelineCentral and AICP	Physical activity	125
Total		**2034**

Abbreviations. ACS: American Cancer Society, AICP: Alliance for the Implementation of Clinical Practice Guidelines, CCS: Canadian Cancer Society, BCRI: British Cancer Research Institute, INCa: French National Cancer Institute.

Table S2. Assessment of guidelines (assessors' scores) and justification.

Guideline ID	AGREE II domains	Items	Score of assessor 1	Score of assessor 2	Comments or justification
Campbell et al. (2019)	Scope and purpose	Item 1	7	6	The context and aim (objective) of the guideline are clearly described. It is easy to find the objectives. The population (cancer patients) to whom the guideline is meant to apply is specifically described.
		Item 2	6	7	The health issue and health outcomes covered by the guideline are described. These are recommendations on physical activity (PA) for cancer survivors in relation to depression, fatigue, anxiety, etc.
		Item 3	5	7	The population to whom the recommendations should be applied are cancer patients (all types of cancer, both sexes).
	Stakeholder involvement	Item 4	6	7	The stakeholders (40 professionals from 20 organizations around the world) involved in the guideline development group are clearly described. The role and affiliations of each participant were presented.
		Item 5	2	1	The target population was not involved in the development of the guideline.
		Item 6	5	4	The description of the target users is not clear. Nevertheless, the main target group for guideline is cancer survivors, health professionals.
	Rigor of development	Item 7	7	7	The methods and strategies used to search the scientific evidence have been clearly described (databases, the key words, the period covered by the search, and the presentation of the search strategy in the appendix).
		Item 8	6	7	The evidence selection criteria are clearly described and presented in Figure 1.
		Item 9	4	5	The methodological strength and limitations of the scientific evidence have not been described. However, the authors described some limitations in the development of the guidelines and suggested directions for future updates.
		Item 10	6	7	The methods used to formulate the recommendations are described. The recommendations were drawn up at consensus meetings (2 round tables at the start) and validation meetings (3 consensus meetings) with discussions between the participants to reach decisions.
		Item 11	6	5	Data on the health benefits, side effects, and specific considerations of PA in cancer survivors have been considered in the recommendation formulation. In addition, a brief discussion about other exercise modalities (e.g., yoga) is provided at the end of the article (see supplementary data).
		Item 12	6	7	Recommendations have been formulated based on scientific evidence (strong and moderate evidence). Each recommendation is linked to a list of evidence references. The different levels of scientific evidence according to the results are presented.
		Item 13	6	6	There is no mention that the guideline was reviewed by external experts. But as it is a scientific article, it is supposed to have undergone a double-blind review.
		Item 14	4	4	The procedure and methodology for updating the guideline is not clearly described. However, guidance on updating has been provided.

	Clarity of presentation	Item 15	6	6	Recommendations are concrete and precise. They identify the target population, the pathology, and the results. The characteristics of PA have been clearly identified, and the precautions and warnings have also been formulated.
		Item 16	5	6	Guideline does not cover a specific outcome. It is applied to a wide range of outcomes: fatigue, depression, anxiety, etc.
		Item 17	6	7	Some of the key information in the recommendations is easily identifiable and presented in Box 3 or Table 5 and grouped together in a single section.
	Applicability	Item 18	6	7	Elements on the tolerance of PA, its practice or implementation (with or without supervision, in or out of hospital), and specific precautions were presented.
		Item 19	5	6	There is no guidance or tools on how the recommendations should be put into practice. Only information about the implementation of guideline has been provided.
		Item 20	2	1	Information on the potential impact of applying the recommendations was not provided (economic evaluation).
		Item 21	2	4	Criteria for evaluating or verifying the application of the recommendations have not been proposed by the guideline.
	Editorial Independence	Item 22	7	7	The development of the guideline has been funded by public bodies which have no influence on the content of the guideline. None of the authors have any conflict of interest.
		Item 23	6	7	The competing interests of the participants have not been described. The guideline development process has been described and we know that decisions are taken by consensus between the participants. At meetings, differences will normally be discussed.
HAS (2019)	Scope and purpose	Item 1	4	5	The aim of the guideline is not clearly described. However, some background information is provided.
		Item 2	5	6	There is information to help understand the clinical issue addressed by the guideline, even if it is not formulated as a question.
		Item 3	5	6	The population to whom the recommendations should be applied is breast, prostate, and colorectal cancer patients. However, this population is not clearly described.
	Stakeholder involvement	Item 4	2	1	There is no information on the group that develop the guideline.
		Item 5	2	1	Information on the opinions and preferences of the target population is n provided.
		Item 6	4	4	Target users have been identified: healthcare professionals and patients.
	Rigor of development	Item 7	2	1	The methods used to develop the guideline (systematic method) are not described.
		Item 8	2	1	The selection criteria are not described.
		Item 9	2	1	The strengths and limitations of the scientific evidence are not presented.
		Item 10	2	1	The methods used to formulate the recommendations are not described.
		Item 11	5	5	The health benefits and side effects are considered and well described in the recommendations.
		Item 12	2	3	There is not enough information to justify an explicit link between the recommendations and the evidence on which they are based.
		Item 13	2	1	The information about external review of guideline is not presented.
		Item 14	2	2	The procedure for updating the guideline is not described.

	Clarity of presentation	Item 15	6	6	The recommendations are precise and unambiguous. The objectives, the target population and the warnings are clearly described.
		Item 16	5	5	The different prescription options are not clearly presented.
		Item 17	6	7	The recommendations are clearly identifiable. They are presented in a table.
	Applicability	Item 18	6	5	Precautions and contraindications are described.
		Item 19	4	5	There is no information on the implementation of the recommendations.
		Item 20	2	1	The guideline does not provide information on the impact of applying the recommendations on resources (economic evaluation).
		Item 21	2	3	The guideline does not propose monitoring and evaluation criteria.
	Editorial Independence	Item 22	5	6	No information is provided on the financing of the development of the guideline. However, the HAS is a public institution whose sources of funding do not pose a problem.
		Item 23	2	1	There is no information about the competing interests of guideline development group members.
Hayes et al. (2019)	Scope and purpose	Item 1	7	6	The context and objectives of the guideline are clearly described. The guideline objective are: (1) recent evidence for exercise in cancer patients; and (2) present the framework for prescribing exercise to patients, with cancer-specific considerations for individualization, specificity, safety, feasibility and progression.
		Item 2	6	7	The health issues covered by the guideline are well described: the recommendations are aimed at cancer patients and concern the prescription of PA, the prescribing framework, and outcomes.
		Item 3	5	7	The target population is cancer patients (all types). Details on characteristics of this population are not presented.
	Stakeholder involvement	Item 4	5	4	The list of participants, their names and areas of expertise are presented at the end of the guideline (in the financing section).
		Item 5	2	1	Information on the participation and preferences of the target populations was not presented.
		Item 6	6	4	The target users of GUIDELINE are clearly identified. They are patients with all types of cancer and healthcare professionals.
	Rigor of development	Item 7	5	5	The method used to search for scientific evidence is not fully described. The databases used are not specified. Only the keywords used, the search equation and the date of the search are presented.
		Item 8	4	5	The evidence selection criteria are not described. Nevertheless, the search equation allows us to identify a number of exclusion criteria.
		Item 9	2	1	The strengths and limitations of the evidence are not defined.
		Item 10	3	3	There is no information on the methods used to formulate the recommendations. Nevertheless, they are based on evidence.
		Item 11	6	5	The benefits and risks of PA were presented in the guideline. Additional data on other pathologies are also presented.
		Item 12	5	7	Recommendations are formulated based on scientific evidence (systematic review).
		Item 13	7	7	The guideline was blindly reviewed by external assessors (see acknowledgement section).

		Item 14	3	4	The procedure for updating the guideline is not specified.
	Clarity of presentation	Item 15	6	7	The recommendations are well formulated and well presented with details on FITT characteristics of the PA and (Table 1).
		Item 16	6	7	Recommendations are also made on the specific features of each patient. (Table 2).
		Item 17	7	7	The recommendations are easy to identify in the guideline. They are presented in 2 tables.
	Applicability	Item 18	6	7	The guideline described the elements and framework for prescribing PA. Prior assessment, initial assessment of patients and specific considerations.
		Item 19	5	6	There is no guidance or additional material published on how the recommendations should be put into practice. However, there are links to advice websites.
		Item 20	2	1	The guideline does not present information on the resource implications of implementing the recommendations (economic evaluation).
		Item 21	3	4	The guideline does not propose criteria for monitoring and evaluating the implementation of the recommendations.
	Editorial Independence	Item 22	6	7	The authors' sources of funding are given in the acknowledgements section.
		Item 23	4	4	No information on the competing interests of the members of the group that developed the guideline.
Cormie et al. (2018)	Scope and purpose	Item 1	6	6	The context and objectives of the guideline are clearly described. The aim is to provide recommendations to healthcare professionals involved in the care of people with cancer on the integration of exercise into the care of cancer survivors.
		Item 2	6	7	The background of guideline is well described. The evidence for the effectiveness of PA in cancer patients and outcomes is also well described. The target population is not well described.
		Item 3	6	7	The guideline recommendations are applied to cancer patients. There is no detailed description of this target population.
	Stakeholder involvement	Item 4	6	6	Information about the guideline development group n is provided and are clearly described. Their names, titles, areas of expertise and organizations to which they belonged are given. Only their role in the development process is not specified. (https://www.cosa.org.au/about-us/who-we-are/cosa-council/)
		Item 5	2	1	The opinions and preferences of the population were not considered in the guideline development process.
		Item 6	6	5	The guideline is aimed at health professionals involved in the management of cancer patients. Representatives of the different professional categories (are present in the expert development group. (https://www.cosa.org.au/about-us/who-we-are/cosa-council/).
	Rigor of development	Item 7	3	2	The guideline was developed based on scientific evidence (after a literature review). Information on the databases used, the period covered by the research and the research strategies is not provided.
		Item 8	2	1	The criteria for selecting scientific evidence are not presented.
		Item 9	2	1	The strengths and limitations of the scientific evidence have not been defined.
		Item 10	6	6	The methods used to formulate were clearly defined: the consensus method, by consulting all

					experts and stakeholders.
		Item 11	5	5	The health benefits, risks, and outcomes of PA in cancer patients are presented, but not on these adverse effects.
		Item 12	4	4	There is insufficient scientific evidence.
		Item 13	5	4	There is no information available to confirm whether the guideline has been evaluated by external experts. Nevertheless, it may be subject to review by the publication journal.
		Item 14	5	4	The guideline was approved by the panel on 18 August 2017. It remains in force for 5 years from that date, before being updated or amended. The methodology of the update procedure has not been described.
	Clarity of presentation	Item 15	5	3	The recommendations are well formulated and the target population (cancer patients) well identified. Only the outcomes to which they apply are not described.
		Item 16	4	3	Details of the prerequisites, framework and specific features are given.
		Item 17	6	5	The recommendations are easy to identify. They are formulated in boxes (1 to 3), in bold for more details.
	Applicability	Item 18	4	3	Elements facilitating the application of guideline are presented: prior medical assessment, supervision, and individualization of PA prescription.
		Item 19	2	1	The guideline does not offer advice on how to implement the recommendations.
		Item 20	2	1	No information on the impact of applying the recommendations (economic evaluation).
		Item 21	2	1	The guideline does not propose any criteria for monitoring or verifying the application of the recommendations.
	Editorial Independence	Item 22	7	7	The guideline was developed with the support of the COSA Council and the Practice and Cancer Group. It is a stand-alone document, the content of which is not influenced by any other authority.
		Item 23	6	7	Competing interests of the authors are not presented. However, the guideline was developed through a consensus process during which the views (agreements and divergences) of the experts would probably be discussed.
Segal et al. (2017)	Scope and purpose	Item 1	7	7	The background and objectives of guideline are clearly described and detailed. The aim of the guideline was to provide recommendations to clinicians on exercise prescription for cancer patients, focusing on the benefits of certain types of exercise, recommendations on screening requirements for new patients and safety issues.
		Item 2	7	7	The health issues covered (cancer) by the guideline are well and explicitly described in the introduction.
		Item 3	7	7	The target population is well described. It consists of adult cancer patients, including those undergoing active treatment and those who have completed their treatment.
	Stakeholder involvement	Item 4	6	7	The development of this guideline was undertaken by the Exercise for People with Cancer Guideline Development Group, a group organized by Cancer Care Ontario's Program in Evidence-Based Care (PEBC). Full details of experts are not provided.
		Item 5	6	7	Patient representatives have been contacted.
		Item 6	6	5	The guideline is used by clinicians involved in cancer patient management. However, patients

					can also use it.
	Rigor of development	Item 7	7	7	Systematic methods (systematic review of existing guidelines and primary studies) were carried out. (Stages 1 and 2). The databases used (Medline, Embase, Cochrane) and the search strategies (keywords) were presented. The periods covered by the search (September 2011 to April 2015) were also reported.
		Item 8	7	7	The selection criteria (inclusion, exclusion) for scientific evidence were reported in step 2 of the method.
		Item 9	2	1	The strengths and limitations of the scientific evidence are not reported.
		Item 10	6	6	The methods used to formulate and validate the recommendations are presented. By two rounds of internal validation, at a meeting of a panel of experts (consensus). The type of consensus methods used are not described
		Item 11	6	5	The health benefits were taken into account in formulating the recommendations. The risks have not been
		Item 12	6	6	The recommendations are based on scientific evidence.
		Item 13	7	7	The guideline has undergone 2 reviews by external experts. A targeted peer review was carried out by a small group of clinical or methodological experts specializing in PA (by questionnaire). The guideline was also distributed to groups of healthcare practitioners (medical oncologists, physiotherapists, physicians, and nurses) in the province of Ontario for feedback.
		Item 14	4	4	The procedure for updating or updating the guideline was not proposed. Only recommendations for future research are made.
	Clarity of presentation	Item 15	7	7	The recommendations are precise and clear without ambiguity (formulated in 6 points).
		Item 16	3	2	The different implementation options are not described.
		Item 17	7	7	The recommendations are easy to identify. They are presented in bold and grouped into 6 points.
	Applicability	Item 18	6	5	The guideline described the facilitating elements (supervision of the PA, prior medical assessment) and the obstacles to be taken into account.
		Item 19	6	5	Guidance on implementing the recommendations was provided in the guideline.
		Item 20	2	2	The repercussions of applying the recommendations have not been described.
		Item 21	3	4	The criteria for monitoring and verifying the application of the recommendations have not been proposed.
	Editorial Independence	Item 22	7	7	The experts have declared that they have no conflict of interest and that the work produced by the PEBC group is independent of the funding body (Ministry of Health).
		Item 23	6	7	The competing interests and differences of the members of the expert group have not been documented. As the guideline was validated by a consensus process, these points can be taken into account.
Rock et al. (2012)	Scope and purpose	Item 1	6	7	The guideline context is well described, and the objectives clearly formulated. The outcomes and target population are well specified.
		Item 2	7	7	The health issue covered by the guideline is the practice of physical activity in cancer patients.

					It has been well explained. The aim is to summarize the scientific evidence and formulate recommendations for the practice of physical activity after a cancer diagnosis.
		Item 3	6	7	Cancer patients are the population to which the recommendations should apply. This population is not well described.
	Stakeholder involvement	Item 4	6	5	The guideline was drawn up by a group of experts in nutrition, PA, and cancer. The names of the experts, their fields of expertise and their affiliating institutions were presented. A description of their role within the group was not provided.
		Item 5	2	1	The opinions and preferences of the target population were not presented
		Item 6	6	5	The target users of the guideline recommendations are clearly defined. They are healthcare workers involved in the care of cancer patients, cancer survivors and their families.
	Rigor of development	Item 7	3	2	The scientific evidence concerning the effects of PA in people with cancer is presented in the guideline. The methodology used (database, search strategy, time period) to identify this evidence is not described.
		Item 8	3	2	The selection criteria are not described.
		Item 9	2	2	The strengths and limitations of the scientific evidence are not described.
		Item 10	2	1	The methods used to formulate the recommendations are not clearly presented.
		Item 11	6	5	The health benefits and risks (specific precautions) of PA have been considered in the guideline and clearly set out.
		Item 12	6	5	The recommendations were formulated based on scientific evidence. There is a gap between the recommendations and the evidence.
		Item 13	7	7	The guideline has been revised and corrected by the American Cancer Society's advisory committee on nutrition and physical activity.
		Item 14	3	4	The procedure for updating the guideline has not been proposed.
	Clarity of presentation	Item 15	6	6	The recommendations are precise and unambiguous. The different age groups for which they are intended are clearly identified (cancer patients aged 18-64 and the over-65s).
		Item 16	6	7	The different options, types of cancer and age groups are considered in formulating the recommendation.
		Item 17	4	5	The recommendations are not easy to identify.
	Applicability	Item 18	5	4	Elements facilitating the application of the guideline (supervision of the PA, in groups) and obstacles (specific precautions) are described.
		Item 19	4	4	Advice on how to implement the recommendations is not provided. However, specific precautions for implementation are presented.
		Item 20	2	1	The repercussions of applying the recommendations are not set out.
		Item 21	3	4	The criteria for monitoring and evaluating the application of the guideline are not proposed.
	Editorial Independence	Item 22	7	7	The name of the funding body has been submitted; it is the American Cancer Society. No commercial support has been accepted in connection with the development or publication of this guideline.
		Item 23	4	4	The competing interests of the experts are not presented. However, information on their conflict of interest has been provided.

Brunet et al. (2012)	Scope and purpose	Item 1	7	7	The context and objective of the guideline are explicitly described. The aim is to provide physicians with practical recommendations for prescribing PA to breast cancer patients who have completed their active treatment.
		Item 2	6	7	The health problem (breast cancer) is defined in the context section.
		Item 3	7	7	The target population is well described. They are (adult) breast cancer patients who have completed their active treatment.
	Stakeholder involvement	Item 4	4	3	The authors of the recommendations are experts in oncology and physical activity. Their affiliations were presented. Their role in the drafting group was not specified.
		Item 5	2	1	The opinions and preferences of the target population were not identified.
		Item 6	5	4	The users of the recommendations are healthcare professionals and breast cancer patients.
	Rigor of development	Item 7	7	7	Systematic review methods were used to search for scientific evidence. The databases used were: Medline, Pubmed, Cinahl, PsycInfo were used as sources. The keywords used in the search strategy were povided.
		Item 8	7	7	The selection criteria (inclusion and exclusion) were clearly described.
		Item 9	5	7	The strengths and limitations of the scientific evidence have not been defined.
		Item 10	4	5	The methods used to formulate the recommendations are not presented.
		Item 11	6	5	The health benefits and risks of PA were taken into account in formulating the recommendations.
		Item 12	7	7	The recommendations were formulated based on scientific evidence (from the systematic review).
		Item 13	5	4	The guideline has not been reviewed by external experts. However, its publication requested peer review from the journal.
		Item 14	2	3	The procedure for updating the recommendations has not been proposed.
	Clarity of presentation	Item 15	7	7	The recommendations are precise, concise, and unambiguous. The target population and the various outcomes to whom the recommendations are applied clearly presented.
		Item 16	6	5	The different clinical situations in which PA is practised are also presented.
		Item 17	7	7	The recommendations are easy to identify. They are presented in a table (Table 5).
	Applicability	Item 18	6	6	Elements facilitating the application of the recommendations are described (prior medical assessment, consideration of patients' state of health, etc.).
		Item 19	2	6	The guideline does not offer any tools or advice for implementing the recommendations.
		Item 20	2	1	The impact of applying the recommendations (valuation of acquisition cost) has not been assessed.
		Item 21	2	2	The criteria for monitoring and verifying the guideline have not been proposed.
	Editorial Independence	Item 22	4	6	The authors of the guideline are affiliated with public bodies. However, the funding bodies were not specified, nor was any information provided on the authors' conflicts of interest.
		Item 23	3	4	The competing t interests of the authors are not presented
Van den Berg et	Scope and purpose	Item 1	6	7	The context of the guide is well explained. The guideline is a guide to medical rehabilitation specializing in oncology. It describes the recommendations for rehabilitation interventions (PA program) for cancer patients.

al. (2011)		Item 2	6	7	The issues or situations covered by the guideline are described. It described 5 situations related to the rehabilitation of cancer patients.
		Item 3	7	7	Guideline is aimed at patients aged 18 and over. It concerns patients during or after cancer treatment with curative intent, and those in the palliative phase of any oncological condition.
	Stakeholder involvement	Item 4	7	7	The guideline was drafted by a committee made up of rehabilitation doctors, physiotherapists, psychologists, nurses, occupational and company doctors, surgeons, internists-oncologists, radiotherapists, occupational therapists, sports physicians, and geriatric specialists. Multidisciplinary. Names, areas of expertise and affiliations have been in supplementary table.
		Item 5	2	2	Information about the preferences of the target population has not been identified.
		Item 6	6	7	The target users are clearly identified. Guideline is aimed at specialist medical rehabilitation professionals (rehabilitation doctors, physiotherapists, psychologists, social workers, occupational therapists).
	Rigor of development	Item 7	7	7	Systematic methods were used to search for scientific evidence. Databases (PubMed Medline, Embase, PsychInfo, CINAHL, PEDRO) and search strategies used were described. The period covered by the search (up to 4 April 2014). Appendix 7 and 8.
		Item 8	7	7	The selection criteria (inclusion/exclusion) following PICO were described.
		Item 9	7	7	The strengths and limitations (the quality of evidence) were described.
		Item 10	6	7	The method for formulating the recommendations was consensus. There is no detailed description of the method.
		Item 11	5	5	Health benefits are taken into account in the formulation of the recommendations. The side effects and risks of PA practice have not been presented.
		Item 12	6	7	The recommendations focus on the side effects of cancer (quality of life, fatigue, physical condition) and are based on the scientific evidence found in the literature.
		Item 13	3	4	It is not clearly stated whether external experts evaluated the guideline. But as it is a scientific article, we assume that it has been peer-reviewed before publication.
		Item 14	3	2	The procedure for updating the guideline is not described.
	Clarity of presentation	Item 15	7	7	The recommendations are precise and unambiguous.
		Item 16	6	6	Some management options were presented (e.g. for patients over 55).
		Item 17	6	7	The recommendations are easy to identify.
	Applicability	Item 18	6	7	Barriers and facilitators to the implementation of the recommendations are described. These include assessing patients' state of health beforehand, taking patients' preferences into account.
		Item 19	5	5	A number of considerations (advice and precautions) have been given to ensure that the recommendations are adapted to the patient.
		Item 20	5	5	Evidence on the cost-benefit assessment of the application of PA was presented.
		Item 21	4	5	Monitoring and evaluation criteria for guideline were not presented.
	Editorial independence	Item 22	6	6	The development of the guideline was funded by a public body. The other members of the Guidelines Working Group were declared that they did not carry out any activities by invitation or with a subsidy from the medical industry.
		Item 23	3	2	The competing interests of the group members were not presented.

McNeely et al. (2006)	Scope and purpose	Item 1	6	7	The objectives of the guideline are clearly formulated. They are formulated around 7 points. Essentially, the aim is to review the literature in order to formulate recommendations for a PA program for cancer patients.
		Item 2	6	7	The issues covered by guideline are described to varying degrees.
		Item 3	5	6	We know from the recommendations that the target population is people with cancer. However, this population is not well described according to their characteristics (age, sex).
	Stakeholder involvement	Item 4	4	4	Information on authors was provided. However, the groups that participated in the development of the guideline were not presented.
		Item 5	2	1	The opinions and preferences of the target population were not identified.
		Item 6	5	4	The target users of guideline are healthcare professionals involved in the care of cancer patients.
	Rigor of development	Item 7	5	6	The results of the literature review were presented in the guideline. The methods by which this scientific evidence were not presented.
		Item 8	3	4	The criteria for selecting scientific evidence are not clearly described.
		Item 9	4	5	The strengths and limitations of the scientific evidence are not presented.
		Item 10	3	4	The methods used to formulate the recommendations are not presented.
		Item 11	5	5	The health benefits and risks of PA were taken into account in formulating the recommendation.
		Item 12	6	6	The recommendations have been drawn based on scientific evidence to which they relate.
		Item 13	5	4	The guideline was assessed by external experts through the publication review process.
		Item 14	3	4	A procedure for updating the guideline has not been described.
	Clarity of presentation	Item 15	6	5	The recommendations are precise and unambiguous. (see Table 2)
		Item 16	5	5	The different options for prescribing PA are clearly set out in the recommendations (before and after treatment).
		Item 17	5	5	The recommendations are less easy to identify.
	Applicability	Item 18	6	7	The elements facilitating the application of the guideline and the obstacles were described.
		Item 19	5	5	Advice is given on how to put the recommendations into practice.
		Item 20	2	1	An assessment of the impact of applying the recommendations (cost-benefit assessment) was not presented.
		Item 21	2	3	Monitoring and auditing criteria have not been proposed by the guideline.
	Editorial Independence	Item 22	5	5	Information on funding sources was presented. The authors of the guideline are funded by public bodies that have no influence on the results.
		Item 23	3	4	The competing interests of the authors have not been described.

Table S3. Raw data from guidelines assessments (assessors' scores and means scores estimates).

AGREE II domains	Items	Campbell et al. (2019)			HAS (2019)			Hayes et al. (2019)			Cormie et al. (2018)			Segal et al. (2017)		
		Assessor 1	Assessor 2	Score/ domain	Assessor 1	Assessor 2	Score/ domain	Assessor 1	Assessor 2	Score/ domain	Assessor 1	Assessor 2	Score/ domain	Assessor 1	Assessor 2	Score/ domain
Scope and purpose	Item 1	7	6	89%	4	5	69%	7	6	89%	6	6	89%	7	7	100%
	Item 2	6	7		5	6		6	7		6	7		7	7	
	Item 3	5	7		5	6		5	7		6	7		7	7	
Stakeholder involvement	Item 4	6	7	53%	2	1	22%	5	4	44%	6	6	56%	6	7	86%
	Item 5	2	1		2	1		2	1		2	1		6	7	
	Item 6	5	4		4	4		6	4		6	5		6	5	
Rigor of development	Item 7	7	7	80%	2	1	19%	5	5	58%	3	2	45%	7	7	75%
	Item 8	6	7		2	1		4	5		2	1		7	7	
	Item 9	4	5		2	1		2	1		2	1		2	1	
	Item 10	6	7		2	1		3	3		6	6		6	6	
	Item 11	6	5		5	5		6	5		5	5		6	5	
	Item 12	6	7		2	3		5	7		4	4		6	6	
	Item 13	6	6		2	1		7	7		5	4		7	7	
	Item 14	4	4		2	2		3	4		5	4		4	4	
Clarity of presentation	Item 15	6	6	83%	6	6	81%	6	7	94%	5	3	56%	7	7	75%
	Item 16	5	6		5	5		6	7		4	3		3	2	
	Item 17	6	7		6	7		7	7		6	5		7	7	
Applicability	Item 18	6	7	52%	6	5	42%	6	7	54%	4	3	17%	6	5	52%
	Item 19	5	6		4	5		5	6		2	1		6	5	
	Item 20	2	1		2	1		2	1		2	1		2	2	
	Item 21	2	4		2	3		3	4		2	1		3	4	
Editorial Independence	Item 22	7	7	96%	5	6	42%	6	7	71%	7	7	96%	7	7	96%
	Item 23	6	7		2	1		4	4		6	7		6	7	
Globale score		5	6	5,50	4	4	4,00	5	5	5,00	4	5	4,50	6	7	6,50
Overall quality		High			Low			Moderate			Moderate			High		
Recommended for clinical practice		**Yes**			No			**Yes**			Recommended with modification			**Yes**		

Table S3. (Continued)

AGREE II domains	Items	Rock et al. (2012)			Brunet et al. (2012)			Van den Berg et al. (2011)			McNeely et al. (2006)			AGREE II mean score (± SD)
		Assessor 1	Assessor 2	Score/ domain	Assessor 1	Assessor 2	Score/ domain	Assessor 1	Assessor 2	Score/ domain	Assessor 1	Assessor 2	Score/ domain	
Scope and purpose	Item 1	6	7	94%	7	7	97%	6	7	94%	6	7	86%	90% (±9%)
	Item 2	7	7		6	7		6	7		6	7		
	Item 3	6	7		7	7		7	7		5	6		
Stakeholder involvement	Item 4	6	5	53%	4	3	36%	7	7	69%	4	4	39%	51% (±19%)
	Item 5	2	1		2	1		2	2		2	1		
	Item 6	6	5		5	4		6	7		5	4		
Rigor of development	Item 7	3	2	46%	7	7	75%	7	7	77%	5	6	58%	59% (±20%)
	Item 8	3	2		7	7		7	7		3	4		
	Item 9	2	2		5	7		7	7		4	5		
	Item 10	2	1		4	5		6	7		3	4		
	Item 11	6	5		6	5		5	5		5	5		
	Item 12	6	5		7	7		6	7		6	6		
	Item 13	7	7		5	4		3	4		5	4		
	Item 14	3	4		2	3		3	2		3	4		
Clarity of presentation	Item 15	6	6	78%	7	7	92%	7	7	92%	6	5	69%	72% (± 12%)
	Item 16	6	7		6	5		6	6		5	5		
	Item 17	4	5		7	7		6	7		5	5		
Applicability	Item 18	5	4	40%	6	6	40%	6	7	71%	6	7	48%	46% (±15%)
	Item 19	4	4		2	6		5	5		5	5		
	Item 20	2	1		2	1		5	5		2	1		
	Item 21	3	4		2	2		4	5		2	3		
Editorial Independence	Item 22	7	7	75%	4	6	54%	6	6	54%	5	5	54%	71% (±21%)
	Item 23	4	4		3	4		3	2		3	4		
Globale score		4	5	4.50	5	6	5.50	6	6	6.00	4	4	4.00	**5.06 (±0.88)**
Overall quality		Moderate			High			High			Moderate			
Recommended for clinical practice		Recommended with modification			**Yes**			**Yes**			No			

RÉSUMÉ

L'activité physique (AP) est l'un des principaux programmes de soins de support recommandés par plusieurs directives pour améliorer les effets secondaires du cancer chez les survivants du cancer, à cause des preuves de son efficacité sur ces issues de santé. Cependant, les preuves de l'efficacité de l'AP sur le retour au travail (RAT) chez les survivants du cancer restent limitées et inconnues. De plus, on ne sait pas si les recommandations d'AP issues des directives existantes sont applicables au RAT après un diagnostic de cancer. L'objectif de cette thèse était d'évaluer les effets des programmes ou interventions d'AP sur le RAT chez les survivants du cancer et de fournir des preuves de l'efficacité de l'AP sur le RAT après un diagnostic de cancer.

Pour répondre à la question de recherche, nous avons utilisé la méthodologie basée sur des preuves (revue systématique, méta-analyse et revue rapide).

Cette thèse a montré que les programmes d'AP sont faisables et sans risque pour les patients atteints de cancer. Nous avons trouvé que les interventions d'AP ont des effets positifs significatifs sur le RAT chez les survivants du cancer. La dose d'AP comprise entre 7,6 et 15 METs.h/semaine, consistant en 100-120 minutes par semaine d'exercices aérobique et de résistance, d'intensité modéré à vigoureux, semblent être efficaces pour améliorer le RAT après cancer.

En conclusion, cette thèse apporte des preuves modérées sur l'efficacité des interventions d'AP sur le RAT chez les survivants du cancer. Elle a également permis d'estimer la dose d'activité physique nécessaire pour améliorer le RAT chez les patients. À partir des résultats, nous avons proposé un guide avec des protocoles pratiques pour prescrire et implémenter des programmes d'AP pour soutenir la RAT chez les patients de cancer du sein.

mots-clés: Activité Physique, Cancer, retour au travail, Synthèse de preuves, Revue systématique, Méta-analyse.

ABSTRACT

Physical activity (PA) is one of the leading supportive care programs recommended by several guidelines to improve most of cancer side-effects experienced by cancer survivors, because of the strong evidence of its effectiveness on these health outcomes. However the evidence on the effectiveness of PA on return to work (RTW) in cancer survivors remains limited and unknown. In addition, it is unknown whether the recommendations from existing PA guidelines are applicable to RTW after cancer diagnosis. Therefore, the objective of this thesis was to evaluate the effects of PA programs or interventions on RTW in cancer survivors and provide evidence for the effectiveness of PA on RTW after a cancer diagnosis.

To address the research question, we used evidence-based methodology (systematic review, meta-analysis, and rapid review).

This thesis showed that PA programs are feasible and safe for cancer patients. We found that PA interventions have significant positive effects on RTW in cancer survivors. The dose of PA comprised between 7.6 and 15 METs.h/week, consisting of 100-120 minutes per week of moderate to vigorous intensity aerobic and resistance exercise, seem to be effective in improving RTW after cancer.

In conclusion, this thesis provides moderate evidence on the effectiveness of PA interventions on RTW in cancer survivors. It also allowed us to estimate the dose of physical activity needed to improve RTW in cancer patients. Based on these findings, we proposed a guidance with practical protocols for prescribing and implementing PA programs to support RTW in breast cancer survivors.

keywords : Physical activity, Cancer, return to work, Evidence synthesis, Systematic review, Meta-analysis.

Présidence de l'université
40 rue de rennes – BP 73532
49035 Angers cedex
Tél. 02 41 96 23 23 | Fax 02 41 96 23 00

université angers

Titre : **Impact de l'activité physique sur le retour au travail après cancer : une approche basée sur les preuves.**

Mots clés : Activité Physique, Cancer, retour au travail, Synthèse de preuves, Revue systématique, Méta-analyse.

Résumé : L'activité physique (AP) est l'un des principaux programmes de soins de support recommandés par plusieurs directives pour améliorer les effets secondaires du cancer chez les survivants du cancer, à cause des preuves de son efficacité sur ces issues de santé. Cependant, les preuves de l'efficacité de l'AP sur le retour au travail (RAT) chez les survivants du cancer restent limitées et inconnues. De plus, on ne sait pas si les recommandations d'AP issues des directives existantes sont applicables au RAT après un diagnostic de cancer. L'objectif de cette thèse était d'évaluer les effets des programmes ou interventions d'AP sur le RAT chez les survivants du cancer et de fournir des preuves de l'efficacité de l'AP sur le RAT après un diagnostic de cancer.

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En conclusion, cette thèse apporte des preuves modérées sur l'efficacité des interventions d'AP sur le RAT chez les survivants du cancer. Elle a également permis d'estimer la dose d'activité physique nécessaire pour améliorer le RAT chez les patients. À partir des résultats, nous avons proposé un guide avec des protocoles pratiques pour prescrire et implémenter des programmes d'AP pour soutenir la RAT chez les patients de cancer du sein.

Title: **Impact of physical activity on return to work after cancer diagnosis: an evidence-based approach.**

Keywords: Physical activity, Cancer, return to work, Evidence synthesis, Systematic review, Meta-analysis.

Abstract: Physical activity (PA) is one of the leading supportive care programs recommended by several guidelines to improve most of cancer side-effects experienced by cancer survivors, because of the strong evidence of its effectiveness on these health outcomes. However the evidence on the effectiveness of PA on return to work (RTW) in cancer survivors remains limited and unknown. In addition, it is unknown whether the recommendations from existing PA guidelines are applicable to RTW after cancer diagnosis. Therefore, the objective of this thesis was to evaluate the effects of PA programs or interventions on RTW in cancer survivors and provide evidence for the effectiveness of PA on RTW after a cancer diagnosis.

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