



RISK AND SURVIVAL OF SECOND PRIMARY TUMORS IN WOMEN'S RELATED CANCERS

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TESE DE DOUTORAMENTO EM SAÚDE PÚBLICA
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“...If you know, you want to know more. If you want to know more, you are alive.”

National Geography Society

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TABLE OF CONTENTS

ABSTRACT.....	5
RESUMO	11
INTRODUCTION.....	17
INCIDENCE, MORTALITY, AND SURVIVAL OF CANCER.....	17
MULTIPLE PRIMARY CANCERS	25
<i>Epidemiology of multiple primary cancers.....</i>	<i>29</i>
<i>Etiology of multiple primary cancers</i>	<i>31</i>
<i>Survival of patients with multiple primary cancers.....</i>	<i>34</i>
CUMULATIVE INCIDENCE AND COMPETING RISKS.....	35
SURVIVAL METHODS	37
OBJECTIVES	39
METHODS.....	41
PAPERS	43
TEMPORAL TRENDS IN THE INCIDENCE OF SECOND PRIMARY CANCERS IN NORTHERN PORTUGAL: A POPULATION-BASED STUDY.....	45
SECOND PRIMARY CANCERS AMONG FEMALES WITH A FIRST PRIMARY BREAST CANCER: A POPULATION-BASED STUDY IN NORTHERN PORTUGAL.....	76
THE CONTRIBUTION OF SECOND PRIMARY CANCERS TO THE MORTALITY OF PATIENTS WITH A BREAST FIRST PRIMARY CANCER	92
RISK AND SURVIVAL OF THIRD PRIMARY CANCERS IN A POPULATION-BASED COHORT OF BREAST CANCER PATIENTS	106
SECOND PRIMARY CANCERS AMONG FEMALES WITH A FIRST PRIMARY CERVICAL, ENDOMETRIAL AND OVARIAN CANCER: A POPULATION-BASED STUDY IN NORTH PORTUGAL.....	115
DISCUSSION.....	147
REFERENCES	149

ACRONYMS AND ABBREVIATIONS

ASIR (W) – Age Standardized Incidence Rate, calculated using the world standard population

ASMR (W) – Age Standardized Mortality Rate, calculated using the world standard population

IACR – International Association of Cancer Registries

IARC – International Agency for Research on Cancer

CI – Confidence Interval

FPC – First Primary Cancer

HDI – Human Development Index

IC – Intervalo de Confiança

KM – Kaplan-Meier

MCPs – Múltiplos Cancros Primários

MPCs – Multiple Primary Cancers

PCP – Primeiro Cancro Primário

PYAR – Person-years at risk

RORENO – Registo Oncológico Regional do Norte

SCP – Segundo Cancro Primário

SEER – The Surveillance, Epidemiology, and End Results

SIR – Standardized Incidence Ratio

SPC – Second Primary Cancer

TIP – Taxa de Incidência Padronizada

TCP – Terceiro Cancro Primário

TPC – Third Primary Cancer

USA – United States of America

ABSTRACT

The increasing number of new cases of cancer, efforts for earlier detection and the use of more effective treatments have contributed to a rise in the number of survivors of cancer at risk of multiple primary cancers (MPCs).

Breast, endometrial, ovarian, and cervical cancers represent nearly 40% of the cancer burden among females worldwide, and account for almost a quarter of the overall mortality. In Portugal, these cancers are responsible for one third of cancers among females. Quantifying the risk and survival of MPCs is particularly important to define surveillance priorities and to manage patient expectations and needs, regarding the burden of survivorship.

Thus, considering the relevant cancers among the female population due to its relatively high survival, high number of MPCs among patients with a previous cancer and that MPCs following an endometrial, ovarian, or cervical cancer diagnosis have not been previously addressed in Northern Portugal, the aims of this thesis were to address the following main research questions:

- A. What are the temporal trends of second primary cancers (SPCs) and standardized incidence ratios (SIRs) among patients diagnosed with a first primary cancer (FPC) in 2000-03, 2004-07 and 2008-11 in Northern Portugal;
- B. What is the risk of SPCs or third primary cancers (TPCs) in Northern Portugal, taking into account the competing event of death, among survivors from female breast, endometrial, ovarian and cervical cancer;
- C. What is the contribution of SPCs to the survival of patients diagnosed with a breast FPC in Northern Portugal.

The objectives of this thesis were accomplished through the analysis of cohorts of patients diagnosed with cancer and registered in the North Region Cancer Registry (RORENO) between 2000 and 2015, using the International Agency for Research on Cancer and the International Association of Cancer Registries rules to define SPCs and TPCs. Unless otherwise specified, synchronous tumors were defined as a tumor diagnosed within two months of the FPC and metachronous as two months after the FPC diagnosis.

1. A cohort of patients diagnosed with an FPC followed for the occurrence of SPCs and vital status;
2. A cohort of patients diagnosed with a breast FPC followed for the occurrence of SPCs, TPCs and vital status;
3. A cohort of patients diagnosed with a cervical, endometrial, or ovarian FPC followed for the occurrence of SPCs and vital status.

The following paragraphs describe the specific objectives of the thesis, along with the corresponding methods and main results:

- 1. To describe temporal trends in the incidence rates and SIRs of SPCs among patients with an FPC (PAPER 1).**

All adult Northern Portuguese residents diagnosed with an FPC between 1 January 2000 and 31 December 2011 were followed until 31 December 2013 for the occurrence of SPCs and vital status. Incidence rates and SIRs were estimated for each period (2000-03, 2004-07 and 2008-11) by sex, and considering the time between FPC and SPC diagnosis.

During follow-up, 10119 (7.4%) SPCs were identified among patients diagnosed with an FPC in 2000 to 2011. The incidence rate of SPCs was over 10-fold higher in the first two months, remaining stable over the follow-up period but increased rates were noted in 2004-07 and 2008-11. Overall, a greater proportion of SPCs was diagnosed among males than females. Additionally, the proportion of SPCs diagnosed appeared to increase with age. Increases in SIRs of SPCs were observed from 2000-03 to 2008-11, ranging from 1.16 to 1.77 and 1.54 to 2.33, among males and females, respectively. This was particularly evident for FPCs and SPCs of the lip, oral cavity, pharynx, esophagus and larynx among males, and colon and rectum, lung, ovary, and cervix among females.

- 2. To estimate the incidence rates and SIRs, as well as the probability of being diagnosed with an SPC among patients with a breast FPC (PAPER 2).**

A cohort of patients with a breast FPC from RORENO, diagnosed between 1 January 2000 and 31 December 2010 was followed to 31 December 2015 for synchronous and metachronous SPCs. The cumulative incidence of metachronous SPCs considering death as a competing event, and incidence rates and SIRs of SPCs were estimated.

The diagnosis of an SPC occurred in 1229 (7.7%) patients with a breast FPC, of which 17.5% were synchronous tumors. SPCs occurred mainly in the breast, followed by digestive organs, lung, thyroid,

and female genital organs. The incidence rate of SPCs was over 14-fold higher in the first few months of follow-up than in the remaining period. Incidence rates remained relatively stable from 12 months on with 1000 SPCs/100000 persons-year. Globally, patients with a breast FPC had a higher incidence for all types of cancer compared to the general female population (SIR = 1.36, 95% confidence interval (CI): 1.28-1.43), and in particular for cancers of the breast (SIR = 1.35, 95%CI: 1.21-1.50), stomach (SIR = 1.29, 95%CI: 1.05-1.57), colon (SIR = 1.43, 95%CI: 1.21-1.68), lung (SIR = 2.04, 95%CI: 1.63-2.52), lymphoma (SIR = 1.43, 95%CI: 1.04-1.91), uterus (SIR = 1.89, 95%CI: 1.50-2.37), and ovary (SIR = 1.56, 95%CI: 1.02-2.29). The 10-year cumulative incidence of metachronous SPCs following a breast FPC was 6.6% and the corresponding 10-year cumulative mortality was 26.2%.

3. To estimate the contribution of SPCs to the mortality of patients with a breast FPC (PAPER 3).

A population-based cohort of patients with a breast FPC diagnosed between 1 January 2000 and 31 December 2010 was followed for SPCs (31 December 2015) and vital status (30 June 2021). Patients diagnosed with an SPC (265 synchronous and 897 metachronous, ≤ 1 and >1 year after the FPC, respectively) were matched (1:3, by five-year age group and year of breast FPC diagnosis) to those without an SPC and alive when the corresponding SPC was diagnosed.

Significantly higher hazards for death were found among patients with an SPC (hazard ratio of 1.56; 95%CI: 1.29-1.89 for synchronous SPCs; and 2.85, 95%CI: 2.56-3.17 for metachronous SPCs) compared to patients with a breast FPC only. Estimates were higher for synchronous lung, stomach, non-Hodgkin lymphoma and breast SPCs, and metachronous liver, stomach, ovary, lung, rectum, corpus uteri, colon, breast, and non-Hodgkin lymphoma SPCs. The 15-year cumulative mortality was 59.5% for synchronous SPCs and 68.7% for metachronous SPCs, which was higher than that in patients with a breast FPC only.

4. To estimate the long-term risk and survival of TPCs among patients with a breast FPC (PAPER 4).

Patients with a breast FPC diagnosed between 1 January 2000 and 31 December 2010 were followed for a TPC (31 December 2015) and death from any cause (30 June 2021). The cumulative incidence of and mortality among TPCs were estimated. To compare survival, female patients with a TPC were matched (1:1, by age group, years between FPC and SPC diagnosis, and SPC location) to FPC + SPC patients without a TPC.

Overall, 67 (0.4% of FPCs and 5.4% of SPCs) TPCs were diagnosed. The most common TPC sites were digestive, breast, and female genital organs. Among all FPCs, the 15-year cumulative incidence (95%CI) of a TPC was 0.69% (0.47-0.90%) and among SPCs, 7.21% (4.99-9.43%). The 15-year cumulative mortality of TPCs and matched patients was 70.0% and 51.5%, respectively. For TPCs, compared to matched SPC only patients, the age-adjusted hazard ratio (95%CI) for death was 2.86 (1.61-5.07).

5. To estimate the incidence rates and SIRs, and as well as the probability of being diagnosed with an SPC among patients with a cervical, endometrial, or ovarian FPC (PAPER 5).

A cohort of patients with cervical, endometrial, or ovarian FPC diagnosed between 1 January 2000 and 31 December 2010 was followed until 31 December 2015 for synchronous and metachronous SPCs. Cumulative incidence of metachronous SPCs considering death as a competing event, and incidence rates and SIRs of SPCs were estimated.

Diagnosis of an SPC occurred in 541 (9.3%) patients, of which 26.6% represented synchronous tumors. A 10-fold higher incidence rate of SPCs was identified in the first two months than in the remaining follow-up period. SPCs were more frequent among patients with endometrial cancers. Colon, breast, and corpus uteri were the most common sites for an SPC among patients with a gynecological FPC. A higher incidence of all (SIR = 1.96, 95%CI: 1.79-2.12) and individual SPCs compared to the general female population was found, with the most relevant sites being colon (SIR = 2.32, 95%CI: 1.82-2.89), lung (SIR = 2.70, 95%CI: 1.88-3.66), cervix (SIR = 4.87, 95%CI: 3.43-6.56), endometrium (SIR = 5.37, 95%CI: 4.16-6.73) and ovary (SIR = 6.06, 95%CI: 4.12-8.37). The 10-year cumulative incidence of a metachronous SPC and mortality for patients with a gynecological FPC were 7.4% and 39.2%, respectively.

This thesis found that survivors of cancer in Northern Portugal had increasing incidence rates of cancer over time, surpassing those of the general population, with distinct patterns observed based on sex and FPC site.

Among the female population with a breast FPC, a higher incidence of SPCs compared with the general female population was observed, with a 10-year cumulative incidence of metachronous SPCs of 6.6% at 10 years. The predominant sites for an SPC included breast, digestive organs, lung, thyroid, and female genital organs. We also found that female patients with a breast FPC diagnosed with a synchronous SPC had a 1.5-fold higher hazard of death while those with a metachronous SPC had almost a three-fold higher hazard of death when compared to patients with a breast FPC only. Moreover, patients with a breast FPC and TPC had a higher probability of all-cause mortality over 15

years compared to those with a breast FPC and SPC only. The most common TPCs occurred in digestive organs, breast, and female genital organs, with a relatively low 15-year cumulative incidence among all patients with a breast FPC.

We also found that SPCs were frequent among patients with a gynecological FPC, who had a 10-year cumulative incidence of SPCs of 7.4%, and the most common sites for an SPC were colon, breast, and corpus uteri. The incidence of SPCs was higher than in the general female population, namely for cancer sites of the colon, cervix, endometrium, and ovary.

This thesis provides an overview of the incidence of SPCs in Northern Portugal and used comprehensive and precise methodologies to estimate the risk associated with MPCs among survivors of specific female cancers. Our findings underscore the significance of a patient's previous cancer history in formulating therapeutic choices and prognostic assessments. Additionally, our work highlights the importance of determining surveillance priorities and effectively managing patient's expectations concerning the burden of cancer survivorship.

O aumento do número de novos casos de cancro, os esforços para uma deteção mais precoce e a utilização de tratamentos mais eficazes contribuíram para um aumento do número de sobreviventes de cancro em risco de múltiplos cancros primários (MCPs).

Os cancros da mama, do endométrio, do ovário e do colo do útero representam cerca de 40% da incidência do cancro nas mulheres em todo o mundo e são responsáveis por quase um quarto da mortalidade global. Em Portugal, estes cancros são responsáveis por um terço dos cancros do sexo feminino. Quantificar o risco e a sobrevivência dos MCPs é particularmente importante para definir prioridades de vigilância e para gerir as expectativas e necessidades dos doentes, no que diz respeito à carga de sobrevivência.

Assim, considerando a relevância dos cancros na população feminina devido à sua sobrevivência relativamente elevada, o elevado número de MCPs entre as doentes com cancro e que os MCPs após o diagnóstico de cancro do endométrio, ovário ou colo do útero não foram previamente abordados no Norte de Portugal, os objetivos desta tese foram abordar as seguintes questões principais de investigação:

- A. Quais são as tendências temporais dos SCPs e das taxas de incidência padronizadas (TIPs) entre os doentes diagnosticados com um primeiro cancro primário (PCP) em 2000-03, 2004-07 e 2008-11 no Norte de Portugal;
- B. Qual o risco de SCP ou de terceiro cancro primário (TCP) no Norte de Portugal, tendo em conta o evento concorrente morte, entre as sobreviventes de cancro da mama, do endométrio, do ovário e do colo do útero;
- C. Qual a contribuição dos SCPs ou TCPs para a sobrevivência das doentes com diagnóstico de PCP da mama no Norte de Portugal.

Os objetivos desta tese foram concretizados através da análise de coortes de doentes diagnosticados com cancro e registados no Registo Oncológico da Região Norte (RORENO) entre 2000 e 2015, utilizando as regras da *International Agency for Research on Cancer* e da *International Association of Cancer Registries* para definir SCP e TCP; foi considerado que os tumores síncronos foram

diagnosticados no espaço de dois meses em relação a um PCP e os metácrónos quando o diagnóstico foi superior a dois meses após um PCP (a não ser que seja especificado de forma diferente):

1. Uma coorte de doentes diagnosticados com um PCP seguida para a ocorrência de SCPs e estado vital;
2. Uma coorte de doentes diagnosticadas com um PCP de mama seguidas para a ocorrência de SCPs, TCPs e estado vital;
3. Uma coorte de doentes diagnosticadas com PCP do colo do útero, endométrio ou ovário seguidas quanto à ocorrência de SCPs e estado vital.

Os parágrafos seguintes descrevem os objetivos específicos da tese, juntamente com os métodos correspondentes e os principais resultados:

- 1. Descrever as tendências temporais das taxas de incidência e das TIPs dos SCPs entre os pacientes com um PCP (ARTIGO 1).**

Todos os adultos residentes no Norte de Portugal diagnosticados com um PCP entre 1 de janeiro de 2000 e 31 de dezembro de 2011 foram seguidos até 31 de dezembro de 2013 para a ocorrência de SCPs e estado vital. As taxas de incidência e as TIPs foram estimadas para cada período (2000-03, 2004-07 e 2008-11), por sexo e considerando o tempo entre o diagnóstico de PCP e de SCP.

Durante o acompanhamento, foram identificados 10119 (7,4%) SCPs entre os doentes diagnosticados com um PCP entre 2000 e 2011 ($n=136382$). A taxa de incidência de SCP foi mais de 10 vezes superior nos primeiros dois meses, mantendo-se estável ao longo do período de seguimento, mas registou-se um aumento das taxas em 2004-07 e 2008-11. Em geral, foi diagnosticada uma maior proporção de SCP entre homens que nas mulheres. Além disso, a proporção de SCPs diagnosticados parece aumentar com a idade. De 2000-03 a 2008-11, observaram-se aumentos nas TIPs dos SCPs, variando de 1,16 a 1,77 e de 1,54 a 2,33, entre os homens e as mulheres, respetivamente. Isto foi particularmente evidente para os PCPs e SCPs do lábio, cavidade oral, faringe, esófago e laringe entre os homens, e cólon e reto, pulmão, ovário e colo do útero entre as mulheres.

- 2. Estimar as taxas de incidência e as TIPs, bem como a probabilidade de ser diagnosticada com um SCP entre doentes com um PCP de mama (ARTIGO 2).**

Uma coorte de doentes com um PCP da mama do RORENO, diagnosticadas entre 1 de janeiro de 2000 e 31 de dezembro de 2010 foi seguida até 31 de dezembro de 2015 para SCPs síncronos e metácrónos. Foi estimada a incidência cumulativa de SCPs metácrónos, considerando a morte como um evento competitivo, e as taxas de incidência e TIPs para um SCP.

O diagnóstico de um SCP ocorreu em 1229 (7,7%) doentes com um PCP da mama, dos quais 17.5% eram tumores síncronos. Os SCPs ocorreram principalmente na mama, seguidos dos órgãos digestivos, pulmão, tireoide e órgãos genitais femininos. A taxa de incidência de SCPs foi 14 vezes superior nos primeiros meses de acompanhamento do que no restante período. As taxas de incidência mantiveram-se relativamente estáveis a partir dos 12 meses com 1000 SCPs/100000 pessoas-ano. Globalmente, as doentes com um PCP da mama tiveram uma incidência mais elevada de todos os tipos de cancro em comparação com a população feminina em geral (TIP = 1,36, intervalo de confiança (IC) a 95%: 1,28-1,43), e, em particular, de cancros da mama (TIP = 1,35, IC a 95%: 1,21-1,50), estômago (TIP = 1,29, IC a 95%: 1,05-1,57), cólon (TIP = 1,43, IC a 95%: 1,21-1,68), pulmão (TIP = 2,04, IC a 95%: 1,63-2,52), linfoma (TIP = 1,43, IC a 95%: 1,04-1,91), útero (TIP = 1,89, IC a 95%: 1,50-2,37) e ovário (TIP = 1,56; IC a 95%: 1,02-2,29). A incidência cumulativa a 10 anos de SCP metácrónos após um PCP da mama foi de 6,6% e a mortalidade cumulativa a 10 anos correspondente foi de 26,2%.

3. Estimar a contribuição dos SCPs para a mortalidade de doentes com um PCP de mama (ARTIGO 3).

Uma coorte de base populacional de doentes com um PCP da mama diagnosticado entre 1 de janeiro de 2000 e 31 de dezembro de 2010 foi seguida para SCPs (31 de dezembro de 2015) e estado vital (30 de junho de 2021). As doentes diagnosticadas com um SCP (265 síncronos e 897 metácrónos, ≤ 1 e > 1 ano após o FPC, respetivamente) foram emparelhadas (1:3, por faixa etária de cinco anos e ano de diagnóstico de PCP da mama) com aquelas sem um SCP e vivas quando o SCP correspondente foi diagnosticado.

Foram encontradas estimativas significativamente mais elevadas de morte entre as doentes com um SCP [razão de *hazard* de 1,56, IC a 95%: 1,29-1,89 para doentes com um SCP síncrono; 2,85, IC a 95%: 2,56-3,17 para doentes com um SCP metácróno] em comparação com as doentes com um PCP apenas da mama. As estimativas foram mais elevadas para os SCPs síncronos do pulmão, estômago, linfoma não Hodgkin e mama, e para os SCPs metácrónos do fígado, estômago, ovário, pulmão, reto, corpo do útero, cólon, mama e linfoma não Hodgkin. A mortalidade cumulativa a 15 anos foi de 59,5% para SCPs síncronos e de 68,7% para SCPs metácrónos, o que foi superior à das doentes com um PCP da mama apenas.

4. Estimar o risco a longo prazo e a sobrevivência de TCPs entre as doentes com um PCP da mama (ARTIGO 4).

As doentes com um PCP da mama diagnosticado entre 1 de janeiro de 2000 e 31 de dezembro de 2010 foram seguidas até à ocorrência de um TCP (31 de dezembro de 2015) e morte por qualquer causa (30 de junho de 2021). Foi estimada a incidência cumulativa e a mortalidade entre doentes com um TCP. Para comparar a sobrevivência, as doentes com um TCP foram emparelhadas (1:1, por grupo etário, anos entre o diagnóstico de PCP e o SCP e localização do SCP) com doentes PCP + SCP sem um TCP.

No total, foram diagnosticados 67 TCPs (0,4% dos PCPs e 5,4% dos SCPs). Os locais mais comuns de TCP foram o aparelho digestivo, a mama e os órgãos genitais femininos. Entre todos os PCPs, a incidência cumulativa (IC a 95%) a 15 anos de um TCP foi de 0,69% (0,47-0,90%) e entre os SCPs, 7,21% (4,99-9,43%). A mortalidade cumulativa em 15 anos dos TCPs e das doentes emparelhadas foi de 70,0% e 51,5%, respetivamente. Para os TCPs, em comparação com as doentes com apenas SCPs, a razão de *hazard* (IC a 95%) para a morte ajustada para a idade foi de 2,86 (1,61-5,07).

5. Estimar as taxas de incidência e TIPs, bem como a probabilidade de ser diagnosticada com um SCP entre doentes com um PCP do colo, endométrio ou ovário (ARTIGO 5).

Uma coorte de doentes com um PCP do colo, endométrio ou ovário diagnosticado entre 1 de janeiro de 2000 e 31 de dezembro de 2010 foi seguida até 31 de dezembro de 2015 para SCPs síncronos e metácrónos. Foi estimada a incidência cumulativa de SCPs metácrónos considerando a morte como evento concorrente, e as taxas de incidência e TIPs dos SCPs.

O diagnóstico de um SCP ocorreu em 541 (9.3%) doentes, dos quais 26.6% eram tumores síncronos. Nos primeiros dois meses foi identificada uma taxa de incidência de SCPs 10 vezes mais elevada do que no restante período de acompanhamento. Os SCPs foram mais frequentes em doentes com cancro do endométrio. O cólon, a mama e o corpo do útero foram os locais mais comuns para um SCP entre as doentes com um PCP ginecológico. Verificou-se uma maior incidência de todos os SCPs e dos SCPs individuais em comparação com a população feminina em geral (TIP = 1,96, IC 95%: 1,79-2,12), sendo os locais mais relevantes o cólon (TIP = 2,32, IC 95%: 1,82-2,89), pulmão (TIP = 2,70, IC a 95%: 1,88-3,66), colo do útero (TIP = 4,87, IC a 95%: 3,43-6,56), endométrio (TIP = 5,37, IC a 95%: 4,16-6,73) e ovário (TIP = 6.06, IC a 95%: 4,12-8,37). A incidência cumulativa a 10 anos de um SCP metácrono e a mortalidade em doentes com um PCP ginecológico foi de 7,4% e 39,2%, respetivamente.

Esta tese concluiu que os sobreviventes de cancro no Norte de Portugal apresentaram taxas de incidência de cancro crescentes ao longo do tempo, ultrapassando as da população em geral, com padrões distintos observados com base no sexo e no local do PCP.

Na população feminina com um PCP da mama, observou-se uma maior incidência de SCPs em comparação com a população feminina em geral, com uma incidência cumulativa de SCPs metácrónos de 6,6% aos 10 anos. Os locais predominantes para um SCP incluíram a mama, os órgãos digestivos, o pulmão, a tiroide e os órgãos genitais femininos. Verificámos também que as doentes com um PCP de mama diagnosticado com um SCP síncrono tinham um risco de morte 1,5 vezes superior e doentes com um SCP metácrónico um risco de morte quase três vezes superior quando comparadas com doentes com um PCP da mama apenas. Além disso, as doentes com um PCP da mama e um TCP, tinham uma maior probabilidade de mortalidade por todas as causas ao longo de 15 anos, em comparação com as doentes com um PCP da mama e SCP apenas. Os TCPs mais comuns ocorreram nos órgãos digestivos, na mama e nos órgãos genitais femininos, com uma incidência cumulativa relativamente baixa em 15 anos entre todas as doentes com PCP de mama.

Verificámos também que os SCPs foram frequentes entre as doentes com um PCP ginecológico, cuja incidência cumulativa a 10 anos foi de 7.4% e os locais mais comuns para um SCP foram o cólon, a mama e o corpo uterino. A incidência de SCPs foi maior que na população feminina em geral.

Os resultados obtidos no Norte de Portugal, com uma estimativa abrangente e precisa do risco associado aos SCPs entre sobreviventes de cancros especificamente femininos, sublinham a importância da história prévia de cancro na formulação de escolhas terapêuticas e avaliações prognósticas. Além disso, destaca a importância de determinar as prioridades de vigilância e de gerir eficazmente as expectativas dos doentes relativamente aos encargos da sobrevivência ao cancro.

INTRODUCTION

This chapter describes in summary the framework of this thesis and is organized based on the following main topics: major indicators for monitoring the burden of cancer in the global and local context - incidence, mortality, and survival; the context on multiple primary cancers (MPCs), definition rules and epidemiology, and finally a discussion on survival methods.

Incidence, mortality, and survival of cancer

Worldwide, the incidence of cancer has increased in the last few decades (Figure 1) (1). Specifically, the number of new cases of cancer doubled, between 2010 and 2019, due to a growing number of cancer diagnoses in emerging countries (namely, Brazil, China, India), and low- and medium-income countries (1). Aging and improvements in life expectancy, and population growth contribute to explain the increasing number of cases of cancer (2). In addition, the demographic and economic changes affecting particularly countries undergoing the emergent transition, have increased exposure to risk factors associated with globalization. Moreover, the efforts made, particularly, in emerging countries for an early detection of cancer are contributing to the higher incidence of cancer observed (2, 3).

In 2020, GLOBOCAN estimated a total of 19.3 million new cancer cases globally, and the absolute number of cancer cases is anticipated to increase to 28.4 million by 2040 (2). This projection reflects the increasing number of cancer diagnosis among high-income countries but predominantly due to cancers diagnosed in countries with emerging economies, mainly related to the rising prevalence of cancer-risk factors, such as smoking, obesity and unhealthy habits (2, 4).

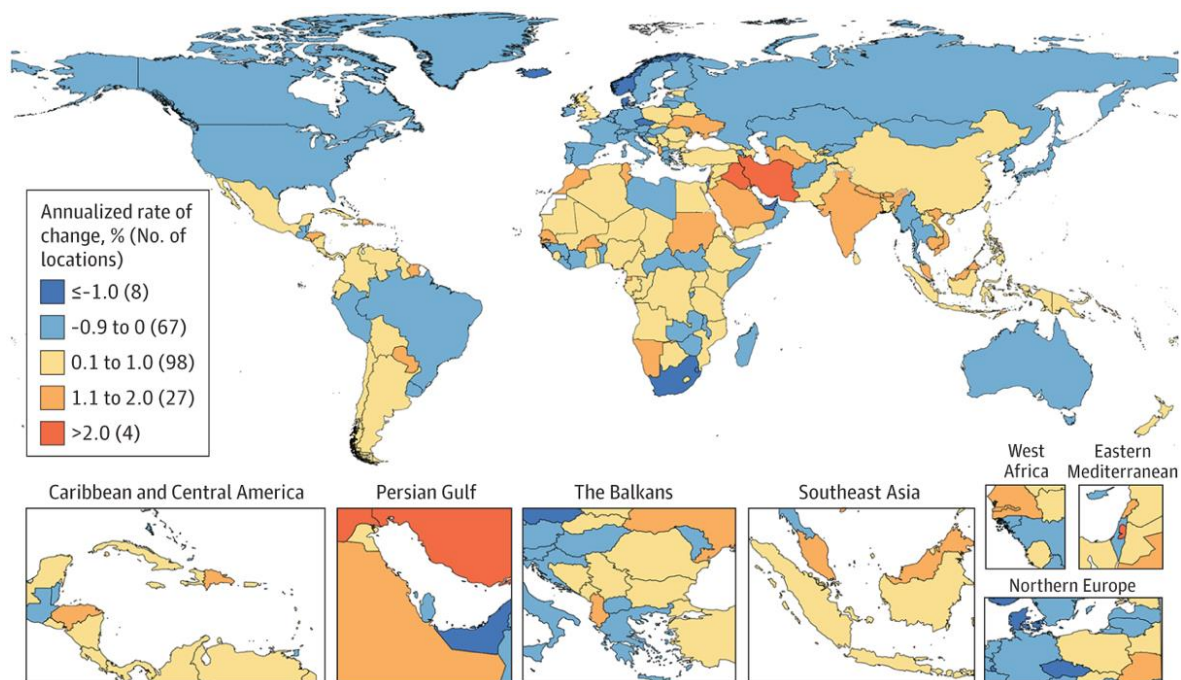


Figure 1. Annualized rate of change in age-standardized, total cancer incidence rate, from 2010 to 2019 in both sexes, (total cancer excludes nonmelanoma skin cancers). Annualized rate of change from 2010 to 2019 represents the average percentage change per year during this period, with negative values indicating decreasing incidence rates and positive values indicating increasing incidence rates. Source: Institute for Health Metrics and Evaluation. Global Burden of Disease (1).

A wide geographic variation in the distribution of new cases of cancer across the world is observed. In 2020, considering both sexes, Asia (where nearly 60% of the population lives) accounted for the highest proportion of incident cases of cancer, approximately 50%, followed by Europe with around 22% incident cases of cancer and America with 20% of incident cases (2). Age-standardized incidence rates per 100000 person-years (ASIRs (W), calculated using the world standard population) were higher with increasing level of a country's Human Development Index (HDI), ranging from 104.3 and 128.0 per 100000 person-years in low HDI countries to 335.3 and 267.6 per 100000 person-years in very high HDI countries, for males and females, respectively (2).

Worldwide, new cancer diagnoses were higher among males, with ASIRs (W) of 222 per 100000 person-years versus 186 per 100000 among females, in 2020. The most diagnosed cancers among both sexes were female breast cancer (11.7%), closely followed by lung (11.4%), colorectal (10.0%), prostate (7.3%), and stomach (5.6%) cancers (Figure 2). Among females specifically, breast cancer is the most diagnosed in 159 countries and cervical cancer is the most common among 23 of the 26 remaining countries (Figure 3). Colon and rectum, lung, thyroid, and corpus uteri are also cancers with a high incidence among females (Figure 2) (2).

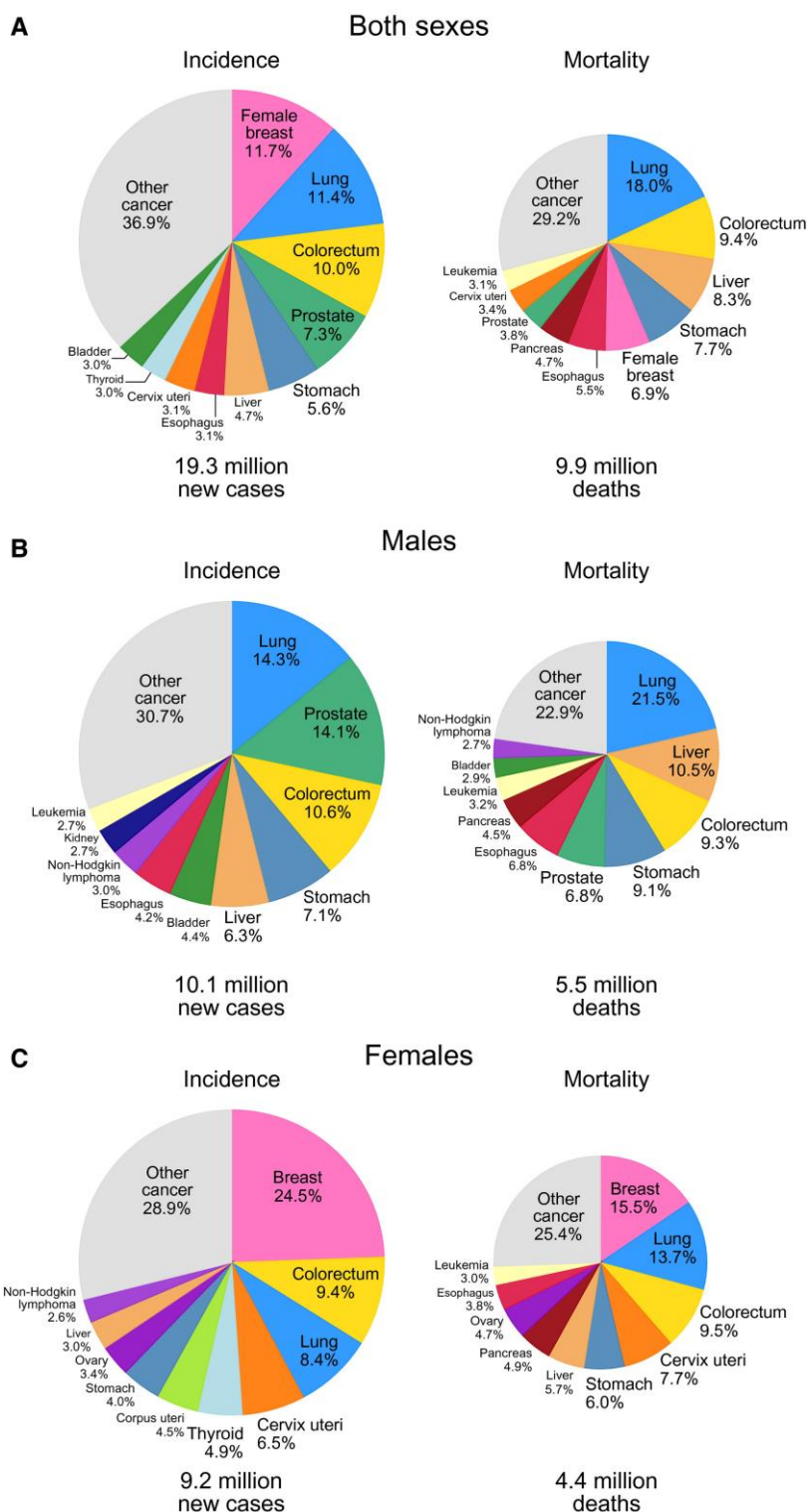


Figure 2. Distribution of cases and deaths for the top 10 most common cancers in 2020 for (A) both Sexes, (B) males, and (C) females. Source: GLOBOCAN 2020 (2).

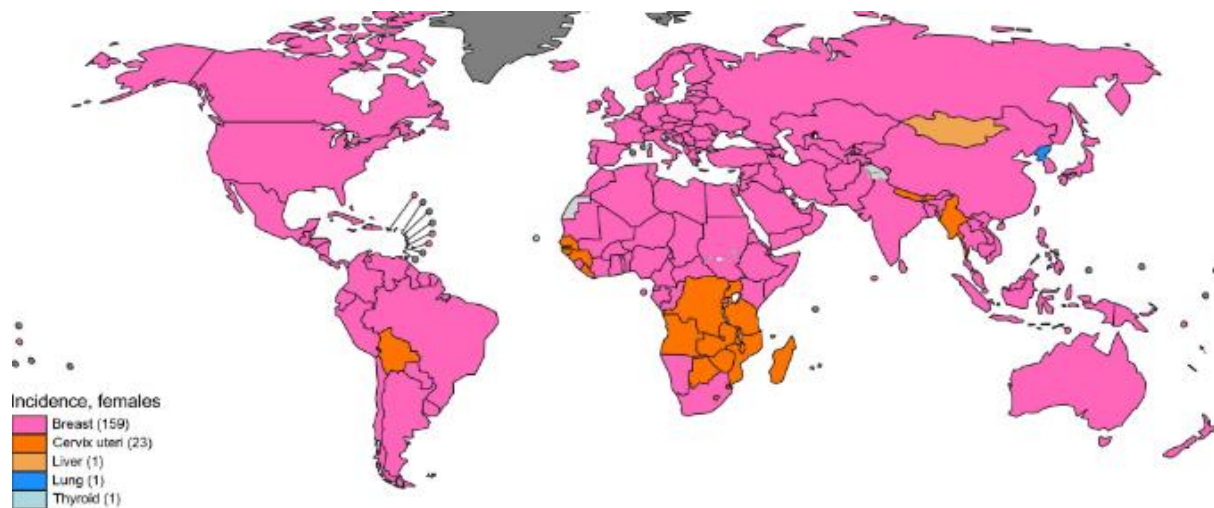


Figure 3. Most common type of cancer incidence in 2020 in each country among females. Source: GLOBOCAN 2020 (2).

Concerning mortality, the number of cancer related deaths also increased in the last decade, as observed in Figure 4, with 10 million cancer deaths estimated in 2019 (1). Mortality from cancer is expected to increase in line with the expected increases in incidence (2), unless an investment on healthcare services fulfills the proper management of cancer and its incidence (5).

Worldwide, age standardized mortality rates (ASMRs (W), calculated using the world standard population) were 120.8 per 100000 person-years for males and 84.2 per 100000 for females in 2020. Considering both sexes, lung cancer was the leading cause of cancer death, accounting for 18.0% of deaths, followed by colorectal (9.4%), liver (8.3%), stomach (7.7%), and female breast (6.9%) cancers, as described in Figure 2 (2). Among females, breast and cervical cancer remain the leading causes of cancer death in 110 and 36 countries (Figure 5), respectively, followed by lung cancer in 25 countries. Colon and rectum, stomach and liver cancers also account for many cancer deaths among females (Figure 2) (2).

By continent, Asia accounts for approximately 50% of cancer-related deaths, followed by Europe with around 20% and America with 14% of cancer-related deaths (2). Considering the HDI of countries, ASMRs (W) were higher in countries in the highest quartile (122.9 to 141.1 per 100000 person-years) versus countries in the lowest quartile (76.7 to 78.0 per 100000 person-years) for males; among females, the variation across HDI levels was lower, in the highest quartile 80.0 to 90.3 per 100000 person-years and in the lower quartile 67.0 to 88.4 per 100000 person-years (6).

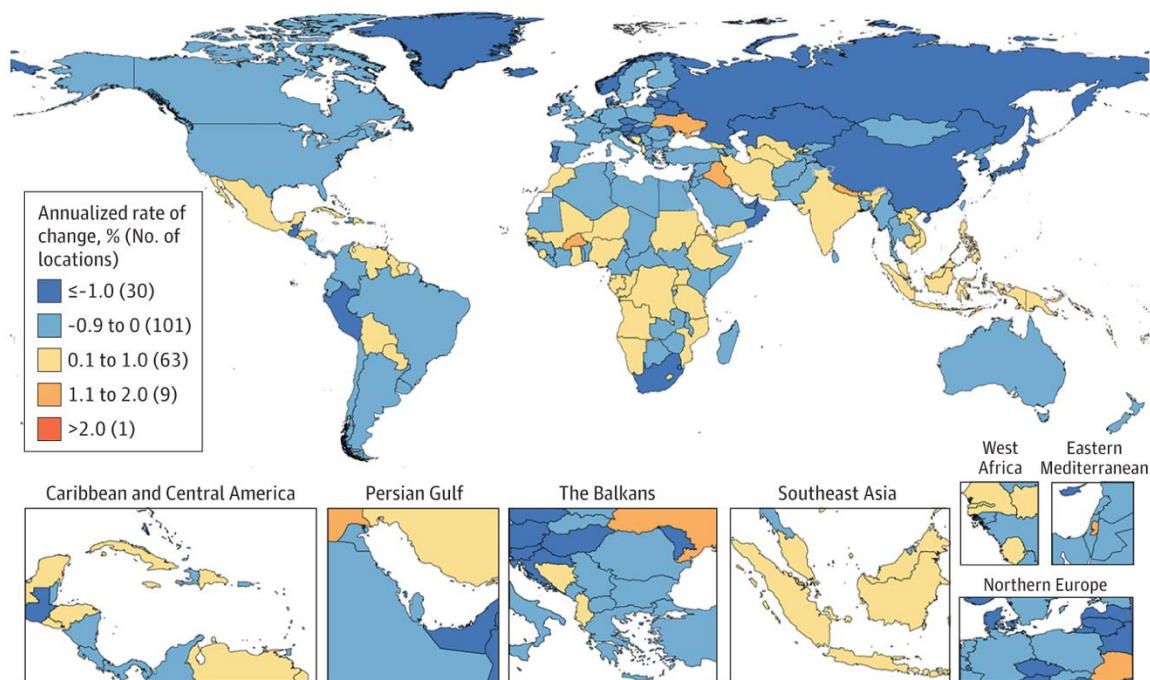


Figure 4. Annualized rate of change in age-standardized total cancer mortality rate, from 2010 to 2019 in both sexes (total cancer excludes nonmelanoma skin cancers). Annualized rate of change from 2010 to 2019 represents the mean percentage change per year during this period, with negative values indicating decreasing mortality rates and positive values indicating increasing mortality rates. Source: Institute for Health Metrics and Evaluation. Global Burden of Disease (1).

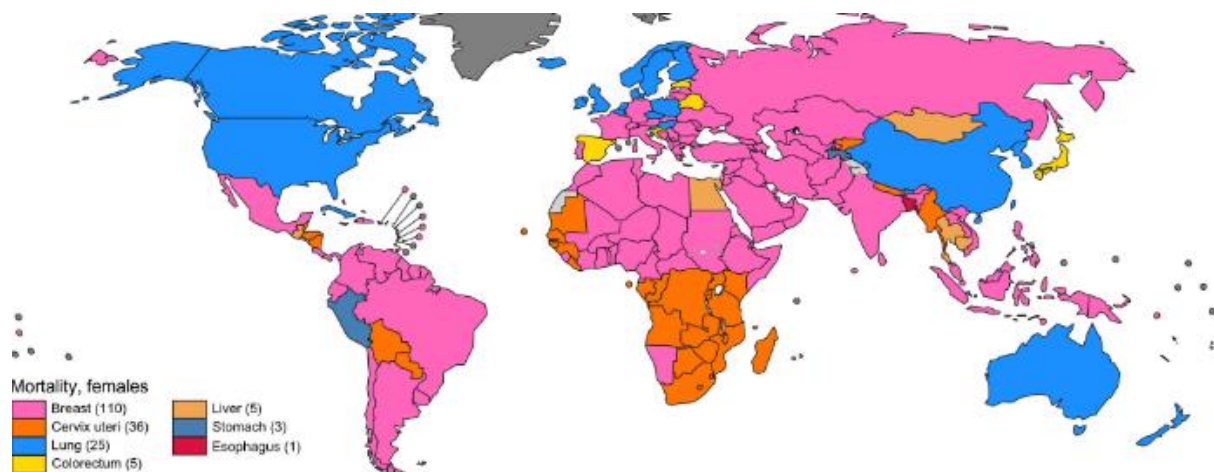


Figure 5. Most common type of cancer mortality by country in 2020 among females. Source: GLOBOCAN 2020 (2).

In Portugal, there has been an increase in the number of cases of cancer of around 20% in 2019 compared with 2010 (7). An increasing trend was observed in ASIRs (W) from 328.4 per 100000

person-years in 2010 to 562.1 per 100000 person-years in 2019. This increase was more remarkable among females (8), despite the incidence of cancer being lower among females (8). The highest incidence rates in both sexes were estimated for individuals aged 80-84 years (ASIR (W) 1687.2 per 100000 person-years), while among females, the highest ASIR(W) was 1256.7 per 100000 person-years for those older than 85 years (8).

Figure 6 shows the ASIR(W) per cancer location in 2020, for both sexes, in Portugal. Digestive organs accounted for the largest number of incident cancers with an ASIR (W) of 140.5 per 100000 followed by genital-urinary and breast cancers (8). For females, breast cancer accounted for nearly a third of cancer diagnoses, followed by thyroid and colon. In Northern Portugal, specifically, the top three incident cancers were breast, colon and lung among females (8).

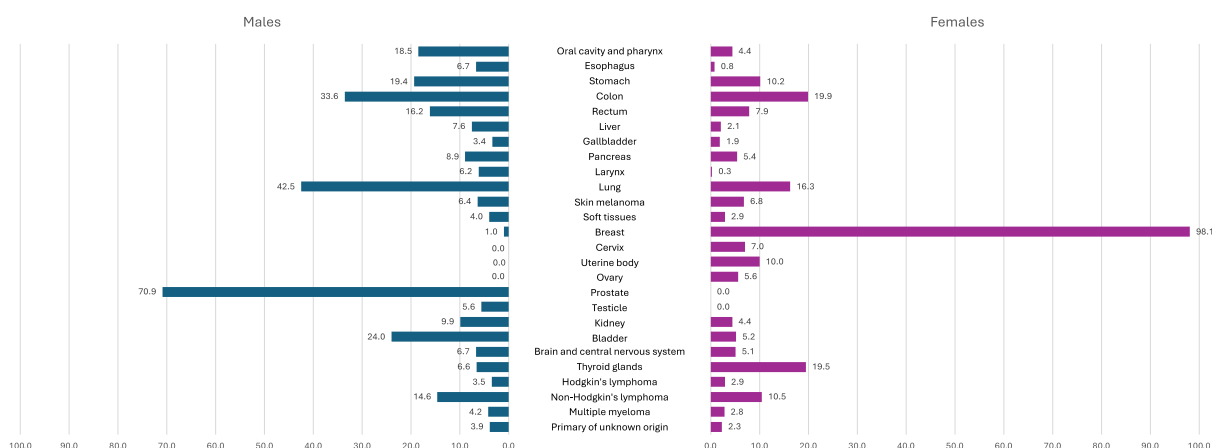


Figure 6. Distribution of the ASIR, using the word standard population, per 100000 person-years, among males and females, in Portugal, in 2020. Source: Registo Oncológico Nacional 2023 (8).

Mortality trends in Portugal follow global trends with an increase in cancer-related deaths (9). In 2020, cancer represented the second cause of death in Portugal, accounting for 30168 deaths (10), corresponding to an ASMR (W) of 103.8 per 100000 person-years for both sexes. The ASMR (W) was considerably lower among females than males (70.9 versus 146.0 per 100000 person-years, respectively) (9, 10). For both sexes, the highest mortality rates were observed for cancers of the lung, colon and rectum, breast, prostate, and stomach (10).

The most recent survival data worldwide was updated in 2015 in the CONCORD-3 project, which compiles the surveillance of cancer survival of 37.5 million patients, from 71 countries and territories, diagnosed with 18 groups of cancer between 2000 and 2014 (11). The CONCORD-3 project data comprises over 60% of the world's population and the included registries collected information from nearly one billion people diagnosed with cancer, almost 14% of the world's population in 2014 (11).

According to the CONCORD-3 project, the five-year net survival is increasing even for some of the more lethal cancers, despite heterogeneity among countries. Overall five-year net survival remains among the highest in the world in North America, Australia and New Zealand, and Finland, Iceland, Norway, and Sweden (11). The five-year net survival was as low as 5% in some countries for some cancer sites, such as liver, pancreas, and lung (11). Efforts in the implementation of early screening, improved treatments and controlling well-known risk factors have led to increasing survival rates in some countries (11-14). Figure 7 shows the global five-year net survival for the most common cancers. Breast and prostate cancers have the highest five-year net survival ranging from 80% to 90%. Nevertheless, there is heterogeneity, for females diagnosed with breast cancer between 2010 and 2014, the estimated five-year net survival is around 90% in the United States of America (USA) and in Australia, and 40% in South Africa (11).

In Europe, the five-year relative survival for females diagnosed with cancer between 2000 and 2007 was 57%. For patients with a breast cancer, the five-year relative survival was 82%, while it was 62% for patients with a cervical cancer, 76% for endometrial cancer and 38% for ovarian cancer (15).

In Portugal, according to the CONCORD-3 project, the five-year age-standardized net survival ranged from approximately 10% for pancreas cancer to almost 90% for prostate cancer for patients diagnosed between 2010 to 2014 (11). By site, esophagus, lung, liver, and pancreas had the lowest five-year net survival (around 10-15%), while thyroid and prostate cancer had the highest survival (over 90%) (11). Among women, the cancers with the best prognosis were those of the thyroid, lip, myeloid disease, chronic proliferative, breast, Hodgkin's disease, kidney and melanoma of the skin; on the other hand, esophagus, liver and pancreas had the worst prognosis (11). Specifically for some female cancers, CONCORD-3 showed a five-year net survival of 85% for breast, 65% for cervix and 40% for ovary cancers (11).

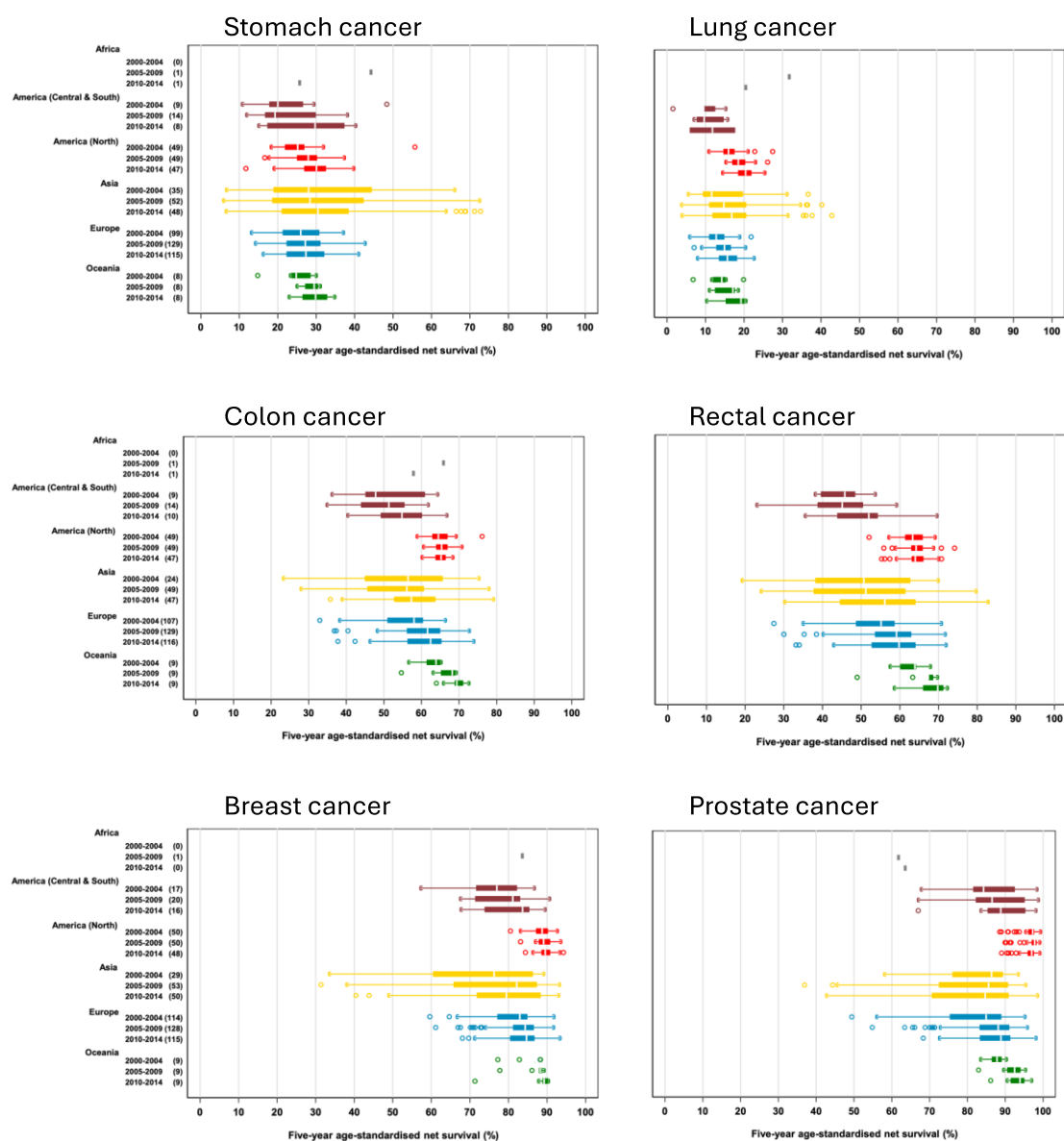


Figure 7. Global range of age-standardized (International Cancer Survival Standard weights) five-year net survival. Source: CONCORD-3 (10).

Multiple primary cancers

First described in 1889 by Billroth, MPCs were understood as “tumors that have a different histological appearance, arise in different locations and produce their own metastatic deposits” (16). In 1921, a report found 4.7% MPCs among 3000 cases of cancer (17) and in 1932, Warren and Gates defined MPCs in accordance with the following criteria: 1) each cancer must be confirmed histologically as malignant; 2) each cancer must be histologically separate and distinct; 3) the new cancer must not be a recurrence or metastasis of the first cancer (18).

For epidemiological studies, tumors are considered MPCs if they arise from a different site and/or are of a different histology or morphology group. Although the definitions for an MPC have changed over time, there are currently two regulations commonly used for coding MPCs by cancer registries: the Surveillance Epidemiology and End Results (SEER) (19) and the International Association of Cancer Registries and International Agency for Research on Cancer (IACR/IARC) (20).

Studies addressing the effect of the application of guidelines from SEER or IACR/IARC, highlight that SEER rules have changed over time (most changes occurred in 2007 and 2018), challenging comparisons of incidence rates and trends analyses. SEER rules consider histology and behavior, site, laterality, and time since diagnosis of a previous primary cancer to define MPCs, while the IARC/IACR rules recommends registering one tumor per organ, regardless of time, unless there are differences in histology (20, 21). Generally, the IARC/IACR rules yield fewer MPCs, particularly cancers that occur in paired organs, at the same anatomic site and with the same or related histologic type, leading to lower incidence estimates (20, 21).

SEER rules, implemented by cancer registries throughout North America, states that cancers should be reported at the same anatomic site and with the same or related histologic type: for example, “each subsite of the colon or each subsite of skin for melanoma is considered a separate primary site” (22). It also considers the laterality of the tumor in the determination of multiple primary cancers: each side is considered a separate site and include a timing rule whereby a second cancer of the same histology in the same cancer site would be considered a second primary: if a tumor is diagnosed in the same site in two months from the diagnosis of the FPC, the tumors are counted as one primary; multiple tumors of the same site are diagnosed more than two months after the FPC, the tumors are classified as a separate primary sites (22).

The latest review of these regulations, the Solid Tumor Coding Rules were published by SEER in 2018, and were revised in 2023, and determined that the Solid Tumor General apply the new rules to head

and neck, colon (includes rectosigmoid and rectum for cases diagnosed 1/1/2018 forward), lung, breast, kidney, urinary sites and central and peripheral nerves; melanoma after 2021; while the 2007 Multiple Primary and Histology Rules instructions are to be used for cases diagnosed 1/1/2007 to 12/31/2022 for other primary sites (22).

The IARC/IACR rules, used for coding in Europe, including Portugal, were published in 2005 and are transcribed below (23):

1. The recognition of the existence of two or more primary cancers does not depend on time.
2. A primary cancer is one that originates in a primary site or tissue and is not an extension, nor a recurrence, nor a metastasis.
3. Only one tumour shall be recognized as arising in an organ or pair of organs or tissue. Some groups of codes are considered to be a single organ for the purposes of defining multiple tumours. These topography code groups are shown in Table 1. Multifocal tumours – that is, discrete masses apparently not in continuity with other primary cancers originating in the same primary site or tissue, for example bladder – are counted as a single cancer.
4. Rule 3 does not apply in two circumstances:
 - 4.1. Systemic (or multicentric) cancers potentially involving many different organs are only counted once in any individual. These are Kaposi sarcoma (group 15 in Table 2) and tumours of the haematopoietic system (groups 8-14 in Table 2).
 - 4.2. Neoplasms of different morphology should be regarded as multiple cancers (even if they are diagnosed simultaneously in the same site).

If the morphological diagnoses fall into one category in Table 2, and arise in the same primary site, they are considered to be the same morphology for the purpose of counting multiple primaries. If the morphological diagnoses fall into two or more of the categories in Table 2, even if they concern the same site, the morphology is considered to be different, and two or more cases should be counted.

Single tumours containing several different histologies which fall into one histological group in Table 2 are registered as a single case, using the numerically highest ICD-O morphology code.

If, however, one morphology is not specific (groups (5), (14) and (17)) and a specific morphology is available, the case should be reported with the specific histology and the non-specific diagnosis should be ignored.

Further, the IARC/IACR rules have the following recommendations for recording (transcribed from the *International rules for multiple primary cancers (ICD-O third edition)* (23):

1. Two tumours of different laterality, but of the same morphology, diagnosed in paired organs (e.g. breast) should be registered separately unless stated to have originated from a single primary.

Exceptions to this rule are:

- a) tumours of the ovary (of the same morphology)
- b) Wilm's tumour (nephroblastoma) of the kidney.
- c) retinoblastoma

which should be recorded as a single bilateral registration when they occur on both sides.

Reminder: Tumours in paired organs of completely different histology should be registered separately.

2. Cancers which occur in any fourth character subcategory of colon (C18) and skin (C44) should be registered as multiple primary cancers.

Table 1. Groups of topography codes considered a single site in the definition of multiple primary cancers.

ICD-O 2/3 Site code	Label	If diagnosed at different times, code first diagnosis. If diagnosed at the same time use codes given below
C01	Base of tongue	C02.9
C02	Other and unspecified parts of tongue	
C00	Lip	C06.9
C03	Gum	
C04	Floor of mouth	
C05	Palate	
C06	Other and unspecified parts of mouth	
C09	Tonsil	C14.0
C10	Oropharynx	
C12	Pyiform sinus	
C13	Hypopharynx	
C14	Other and ill-defined sites in lip, oral cavity and pharynx	
C19	Rectosigmoid junction	C20.9
C20	Rectum	
C23	Gallbladder	C24.9
C24	Other and unspecified parts of biliary tract	
C33	Trachea	C34.9
C34	Bronchus and lung	
C40	Bones, joints and articular cartilage of limbs	C41.9
C41	Bones, joints and articular cartilage of other and unspecified sites	
C65	Renal pelvis	C68.9
C66	Ureter	
C67	Bladder	
C68	Other and unspecified urinary organs	

Transcribed from *the International rules for multiple primary cancers (ICD-O third edition)* (23). ICD-O International Classification of Diseases for Oncology.

Table 2. Groups of malignant neoplasms considered to be histologically ‘different’ for the purpose of defining multiple primary tumours (adapted from Berg JW. Morphologic classification of human cancer. In: Schottenfeld D & Fraumeni JF Jr. Cancer Epidemiology and Prevention, second edition, Chapter 3 of Section 1: Basic Concepts. Oxford, New York: Oxford University Press; pp. 28–44).

Group		
Carcinomas		
1.	Squamous and transitional cell carcinoma	8051-8084, 8120-8131
2.	Basal cell carcinomas	8090-8110
3.	Adenocarcinomas	8140-8149, 8160-8162, 8190-8221, 8260-8337, 8350-8551, 8570-8576, 8940-8941
4.	Other specific carcinomas	8030-8046, 8150-8157, 8170-8180, 8230-8255, 8340-8347, 8560-8562, 8580-8671
5.	Unspecified carcinomas (NOS)	8010-8015, 8020-8022, 8050
6.	Sarcomas and soft tissue tumours	8680-8713, 8800-8921, 8990-8991, 9040-9044, 9120-9125, 9130-9136, 9141-9252, 9370-9373, 9540-9582
7.	Mesothelioma	9050-9055
Tumours of haematopoietic and lymphoid tissues		
8.	Myeloid	9840, 9861-9931, 9945-9946, 9950, 9961-9964, 9980-9987
9.	B-cell neoplasms	9670-9699, 9728, 9731-9734, 9761-9767, 9769, 9823-9826, 9833, 9836, 9940
10.	T-cell and NK-cell neoplasms	9700-9719, 9729, 9768, 9827-9831, 9834, 9837, 9948
11.	Hodgkin lymphoma	9650-9667
12.	Mast-cell tumours	9740-9742
13.	Histiocytes and Accessory Lymphoid cells	9750-9758
14.	Unspecified types	9590-9591, 9596, 9727, 9760, 9800-9801, 9805, 9820, 9832, 9835, 9860, 9960, 9970, 9975, 9989
15.	Kaposi sarcoma	9140
16.	Other specified types of cancer	8720-8790, 8930-8936, 8950-8983, 9000-9030, 9060-9110, 9260-9365, 9380- 9539
17.	Unspecified types of cancer	8000-8005

Transcribed from the *International rules for multiple primary cancers (ICD-O third edition)* (23). NOS not otherwise specified.

According to the time from the diagnosis of the FPC, MPCs are classified as synchronous or metachronous tumors. SEER recommends using a two-month period to distinguish between synchronous and metachronous MPCs (24); however other periods have been used to distinguish synchronous versus metachronous in different studies, such as one, three, six or 12 months after the FPC diagnosis (25).

Epidemiology of multiple primary cancers

The number of patients with MPCs is increasing due to demographic changes (population growing and ageing), higher survival, as a result of better access to screening and diagnostic tests and healthcare in general, as well as improved surveillance of patients with cancer (20, 26). Understanding the occurrence and survival of MPCs is of particular relevance and may help in defining priorities in clinical practice: managing two active malignancies or a past malignancy challenges the staging, treatment choices, and toxicities and interactions, impairs enrollment in research protocols, impacts healthcare services and may negatively impact the expectations of patients with cancer (20, 27, 28).

In epidemiological studies, the frequency of MPCs is reported to range from 2% to 17% (20, 26). A systematic review on the temporal trends of MPCs showed an increasing trend for SIRs when analyzing studies from the USA (1973-2000) and Australia (1982-2001) (25). Specifically, an increasing trend in SIRs was observed between 1973 and 1979 ($SIR=1.12$) and 1995 and 2000 ($SIR=1.21$) in the USA (24). A study from Australia, which included over 200000 cancer survivors, found that SIRs increased from 1.14 to 1.46 between 1982 and 2001 (29). In Europe, SIRs for SPCs have remained stable from 1978 to 2010 in Italy during a mean follow-up time of 14 years (30), while no significant changes were observed for patients diagnosed with a first cancer between 1989 and 2004, and followed up until December 31, 2004, in France (31). The incidence of MPCs generally increases with age, varies across cancer sites, is higher in men than in women, and has linearly increased over time (25). The excess of SPCs differs by cancer site and is reported to range from 1% up to 16%, as observed in Figure 8 (32).



Figure 8. Trends on incidence on SPC (1975–2003) for top 10 sites, SEER. A-Males, B-Females. Reproduced from Hayat et al. (32).

Several factors may explain the differences observed in data for MPCs between registries, namely incidence, trends, and cancer sites. The first is the criteria used by the registry to define MPCs, as previously described. Generally, incidence rates using the SEER rules are higher when compared to incidence rates if IARC/IACR rules are applied. Specifically, female breast, lung and bronchus, and colon cancers may be overestimated – SEER rules generally allow more MPCs to be reported at the same anatomic site and with the same or related histologic type (21, 33). Different methodologies used across studies by including or excluding synchronous tumors, may also influence estimates. A previous study in Portugal showed that the FPC topographies with the highest incidence rates of SPCs in the first two months corresponded to the lowest incident rates in the remaining period of analysis. The exclusion of synchronous tumors, contributed to an underestimation of the incidence rates after the first two months (32, 34). Moreover, the registry operating time also impacts the number of MPCs identified; the proportion of MPCs in older European registries is around 10-13% of all registered tumors, while registries with 10 years or less of observation showed a lower proportion of MPCs depending on the lengths of their activities (21, 26). Modifying healthy habits through campaigns may

also lead to significant changes in the prevalence of risk factors, potentially impacting the cancer incidence among cancer survivors (20, 33, 35). Moreover, the increasing sensitivity of diagnostic tools, as well as the implementation of screening programs (36) and innovations of medical imaging technologies could affect cancer incidence (37). Previous studies have reported that genetic factors, behavioral influences, lifestyle, and comorbidities generally influence patient outcomes (20, 27, 32).

Etiology of multiple primary cancers

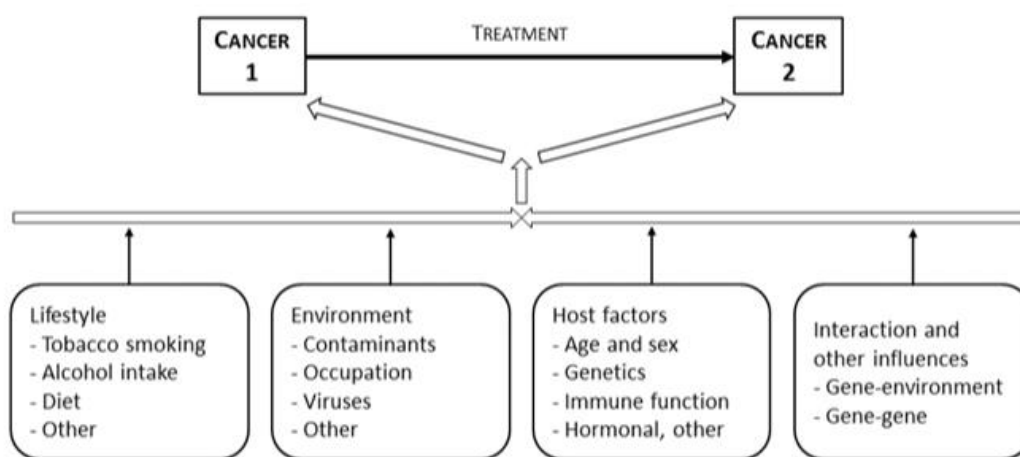


Figure 9. Schematic illustration of risk factors for multiple primary cancers. Reproduced from Travis et al. (38).

MPCs are a consequence of a multi-step and complex process that requires the accumulation of changes in cell signaling, defense mechanisms and the tissue microenvironment (39). Therefore, the risk of a new cancer will be determined by doses of carcinogens and the person's individual susceptibility, which is influenced by age, sex, genetics, ethnicity, as depicted in Figure 9 (20, 28, 38, 40).

Inherited cancer syndromes. Certain inherited mutations in genes responsible for cell cycle control and DNA repair can explain 3% to 10% of all cancers diagnosed annually. However, the majority of tumors (90% to 97%) are non-hereditary and can be attributed mostly to the environment and lifestyle influences (40). Moreover, the penetrance for genetic mutations is variable. Conditions, such as Lynch syndrome, familial adenomatous polyposis, and von Hippel-Lindau disease, are associated with an increased risk of developing multiple types of cancer throughout a patient's lifetime (28, 40). Lynch syndrome or hereditary non-polyposis colorectal cancer which involve a DNA mismatch repair defect in the genes MLH1, MSH2/6 or PMS2 (41). These syndromes have been described as increasing the

risk of colon cancer by around 50% to 80% in a lifetime, endometrial cancer by 60% in a lifetime, as well as ovary, small intestine, brain, skin and urinary tract (42).

The tumor suppressor genes BRCA 1/2 have a role in the error free repair of DNA double-strand breaks and increase the risk of developing particular types of epithelial malignancies, namely breast and ovarian cancer (43). BRCA 1/2 mutations have been found to be responsible for between 5% to 10% of breast cancer cases overall (44). The BRCA 1/2 gene mutation is also associated with second primary breast and male breast cancer, as well as cancers of the ovary, prostate and pancreas (45).

Lifestyle factors. Several factors are implied in carcinogenesis. Tobacco smoke is proven to contain carcinogenic mutagens (46) and as well alcohol (47); these two factors are estimated to be responsible for 35% of all excess risk of MPCs, and are risk factors for oral cavity, pharynx, esophagus, larynx and lung (24). The occurrence of a subsequent tobacco- or alcohol-related cancer has been mainly linked to these habits before the diagnosis of an FPC (48). The consumption of high-caloric and fatty food has been observed to increase the risk of cancer to some extent varying by type of cancer (49). Obesity and excess body weight, has been related to the risk of subsequent primary cancers, to survivors of breast cancer (50). A heavy intake of red and processed meat has been reported to increase the risk of colorectal cancer and is suggested to be associated with cancer of the stomach, esophagus and pancreas (51).

Infections. Infectious agents, such as hepatitis B and C viruses, *Helicobacter pylori* or human papillomaviruses are also well-known risk factors for specific cancers, and are estimated to be associated with 13.0% of cancers diagnosed worldwide (52). Human papillomaviruses are associated with 5% of all cancers, which could represent around 400000 deaths annually (2, 52, 53). The persistent effect from the high oncogenic risk of certain genotypes of human papillomaviruses in distinct anatomical sites (tropism), where they cause pathogenic lesions explain the affection of a range of body sites, including cervix, vulva, vagina, penis, anus and oropharynx (54).

Environmental and occupational exposures. Exposure to certain toxins, from agriculture and industry pollutants, such as asbestos and certain chemicals, are related with the risk of developing certain types of cancer, such as mesothelioma (28, 40). Exposure to solar UVR is related with the burden of melanoma and other non-melanoma skin cancers (55).

Hormonal factors. Hormonal agents, such as hormone replacement, are associated with an increased risk for several cancers, including breast, ovarian, uterine, and prostate cancers. Moreover,

reproductive factors, including age at birth of first child, at menarche and at menopause, and parity, are associated with the risk of developing reproductive-related cancers (20, 38, 40).

The hormonal-dependent cancers of the breast are the most common diagnosed in women, accounting for 75% of new cases of breast cancer (56). Human chorionic gonadotropin binds specifically to luteinizing hormone receptors, which induces the proliferation of MCF-7 breast cancer cells and the differentiation of MCF-7 stem cells (57). Data also suggests that high dietary cholesterol consumption is associated with an increased risk of breast cancer because cholesterol acts as an endogenous ligand for estrogen-related receptors and activates several mechanisms for breast cancer (58). Endometrial cancer is a frequent cancer among females and it is a classic organ dependent on estrogens and progestogens; gonadotropin-releasing hormone, as part of an autocrine system regulating proliferation, the cell cycle, and apoptosis is implicated in endometrial cancer (59). Ovary is also regulated by gonadotropin-releasing hormone, through pituitary secretion, causing proliferation of ovarian cells and could stimulate cancer cells (60).

Previous cancer treatment. Radiation and chemotherapy could modify the coding for genetic polymorphisms in genes encoding enzymes that participate in drug metabolism, such as glutathione S-transferase, cytochrome P450 or thiopurine methyl transferases (28, 40). Radiation is recognized as a cause of cancer since studies on the health effects of radiation on survivors following the atomic bomb and exposure from radiotherapy for cancer or other diseases. Radiation is identified as a risk factor for acute myelogenous leukemia, chronic myelogenous leukemia, and acute lymphoblastic leukemia, and is related with the area exposed and the doses administered (61). A risk of solid tumors after radiotherapy has also been described and the area of application is the most important since the subsequent tumor frequently develops in contiguous areas. Most of these cancers develop after 10 years from the therapy and include lung cancer, thyroid cancer, bone sarcoma, and gastrointestinal or related cancers (stomach, liver, colorectal, and pancreatic) (61).

Chemotherapy was also associated with subsequent cancers, namely, myelodysplastic syndrome and acute myelogenous leukemia and the risk is increased with higher drug doses, longer treatment time, and higher dose-intensity (61).

Tamoxifen is a selective estrogen receptor modulator, and it has two main indications for breast cancer: reducing incidence among patients with the BRCA 1/2 mutation, and it prolongs survival and recurrence-free survival (62, 63). Because of its therapeutic effectiveness, tamoxifen has become a standard adjuvant therapy in breast cancer (64). Despite the antiestrogen effect on breast cancer, tamoxifen has partial estrogen agonist activity in the endometrium, bone, and cardiovascular system

(65), and it was associated with endometrial proliferation, hyperplasia, polyp formation, invasive carcinoma, and uterine sarcoma, with their risk being two or three times higher than that of an age-matched population (66).

Prolonged immunosuppression. Patients with weakened immune systems, conditioned by inheritance, infections or organ transplant are at increased risk of developing certain types of cancer, such as skin, lung, and head and neck cancers (28, 40).

Survival of patients with multiple primary cancers

With the increasing numbers of patients with MPCs, survival from subsequent cancers is a concern, since these patients usually have a poorer prognosis (67, 68). Predicting the survival of patients with MPCs is generally challenging, considering variables involved, such as hereditary, socio-demographics (*e.g.*, gender, age, education level, and ethnicity), lifestyle, and environmental factors (69), primary cancer site, cancer stage, year of initial cancer diagnosis, and time interval between index and subsequent primary cancers (69, 70). Rosso and colleagues addressed this issue among patients with multiple cancers from Europe and found that comparisons of survival depend on the proper identification of a subsequent cancer following a previous prevalent cancer and the operative time of the cancer registry (26).

Few studies have evaluated survival among patients with MPCs. Overall, five-year survival was higher among patients diagnosed with a metachronous SPC compared with patients with a synchronous SPC or an FPC, reflecting probably the pattern of initial tumor in terms of prognostic (70). Moreover, the longer the time since the first index primary to the SPC, the better the survival, especially if the interval exceeds five years (70). The survival of patients with MPCs is also related with the site of the SPC. For breast cancer in particular, the highest survival was noted for bilateral breast cancer when the SPC was diagnosed at least five years after the original primary cancer, with five-year and 10-year survival rates of 100% and 96%, respectively (71). Previously, in Northern Portugal, a population-based evaluated SPCs after any FPC and found the prognosis of patients diagnosed with an SPC shortly after an FPC primarily depended on the type of FPC (72). In contrast, for patients diagnosed with an SPC after a prolonged period following the initial FPC, survival outcomes were influenced by the specific site of the SPC.

Cumulative incidence and competing risks

Understanding the dynamics of occurrence and survival of SPC is of particular importance, especially in the context of an increasing number of survivors from cancer. Considering the occurrence of an SPC, the individual could have a competing event, such as death, hindering the probability of occurrence of the primary outcome of interest. This needs to be considered when estimating the cumulative incidence.

Cumulative incidence of an event is often of interest in medical research. According to the Dictionary of Epidemiology, cumulative incidence or incidence proportion is defined as “incidence expressed as a proportion of a cohort or a group at risk. A risk measure.” (73). It is obtained by dividing the number of new cases during a specific time period by the population at risk at the beginning of the study and it corresponds to the probability or risk of an individual of the population developing the disease of interest over a specific period of time (73). As a value of an incidence proportion, it ranges between 0 and 1, and the time period to which it applies must be specified, otherwise it is not interpretable (74).

When applied to a closed cohort, the analysis is easily done; however, in clinical research that involves time-to-event endpoints (i.e., all-cause mortality), several limitations such as losses to follow-up, censoring for some outcomes may be an issue. If the event of interest is cancer-specific mortality, a patient may die due to causes unrelated to the disease; such events are termed “competing risk events”. Research may also focus on non-mortality related outcomes, such as incidence of disease recurrence, SPC or survival analysis. In these circumstances, death without the observation of the event of interest should be considered a competing risk event. Thus, the competing events could modify the probability of occurrence of the event of interest or even preclude its onset and therefore, statistical methods have been developed to assess time-to-event outcomes in the presence of competing risks (75, 76). In this way, for proper oncologic research, the recognition of competing risks is important.

The understanding of censoring is also important in survival data analysis. When death is the event of interest, then the time of the event is censored for those subjects who are still alive at the end of the study; in a follow-up study, individuals who drop out are censored, because they are lost to follow-up and the time of the occurrence of their event is unknown. For conventional statistical methods for survival analysis, it is important that the assumption of independent or noninformative censoring; which means that, at a given point in time, individuals who remain in the follow-up have the same future risk for the occurrence of the event as those subjects no longer being followed (either because of censoring or study dropout), as if losses to follow-up were random and thus noninformative (77).

The non-parametric Kaplan-Meier (KM) estimator is generally used (75). The KM method gives an estimate of the observed survival probability of an event of interest and the cumulative incidence can then be calculated as one minus this survival probability (1-KM).

In this context, Fine and Grey have identified three distinct problems that arise in the analysis of competing risks data, identified above (78): 1 The estimation of the dependence of the rate of cause-specific death on a set of covariates; 2. The study of the relationship between different causes of death; 3. The estimation of mortality rates given the removal of competing risks.

In the presence of competing events, the 1-KM cannot estimate the cumulative incidence of each event of interest as it overestimates the cumulative probability of a cause-specific failure (75, 76). Therefore, the cumulative incidence function should be used to estimate the cumulative probability when competing risks are present.

Survival methods

The prognosis of cancer is measured by survival statistics, reflecting the course of cancers for patients, clinicians, researchers, and decision-makers. Survival is also used as a policy to measure the lethality of cancer and to compare outcomes across different populations and time periods, and to measure disparities in healthcare access (68).

In an oncologic epidemiological setting, survival is the number alive among people with cancer in a defined population area; it is the chance that a cancer patient will be alive some years (typically five years) after diagnosis (68).

The overall survival, also called all-cause, observed or crude survival, is the most used survival measure as it estimates the proportion of individuals alive at a certain time, after the diagnosis. It describes the survival experience of a group of individuals and uses death from all causes as the endpoint of interest, instead to death from a specific cause (68).

Cancer-specific survival is a survival calculation representing cancer survival if other causes of death were absent. It corresponds to the proportion “number of alive patients with cancer at five-years after the diagnosis” and the “number of patients with cancer”, censoring patients who die from other cancer, other than the specific cancer and it is seldom utilized, because cause of death information is often unreliable, unknown or unavailable (68, 79).

Net-survival is defined by the chance of surviving a cancer, after removing the effects from competing causes of death, including cancer-specific and cancer-consequence deaths (68). In this way, it evaluates the cancer biology and measures the effectiveness (in cancer registries) of cancer interventions. Differences in cancer survival will reflect differences in cancer rather than competing causes of death (68), not influenced by changes in mortality from other causes of death, allowing for comparisons between different groups (*e.g.*, socioeconomic and ethnic groups, or different regions) and also temporal trends (80, 81). Relative survival measures the cancer prognosis in population-based registries and it is the ratio of overall survival of cancer patients divided by the expected survival of a comparable group of general population, without consideration of cause of death information (68, 82).

Different methodologies have been described to estimate relative survival and include: Ederer I (83), Ederer II (84) and Hakulinen (85), and provide similar estimates (68). Another methodology was proposed for estimating net survival in 2012, the Pohar-Perme (86), which considers that the time

from death to the disease and the time from death to other causes are conditionally independent, resulting in unbiased estimates but presenting issues for small samples or extended long term-survival (82, 87, 88).

OBJECTIVES

The increasing number of new cancer cases, efforts for earlier detection and the use of more effective treatments have contributed for a rise in the number of cancer survivors at risk of a subsequent primary cancer. Quantifying the risk and survival of patients with MPCs has a particular importance to define surveillance priorities and to manage patient expectations and needs, regarding the burden of survivorship.

Breast, endometrial, ovary and cervical cancers represent nearly 40% of the cancer burden among females worldwide, and account for almost a quarter of the overall mortality (89). In Portugal, these cancers are responsible for one third of female cancers (8). Despite the considerable cancer burden in women, literature is scarce regarding MPCs among female-specific cancers.

Thus, considering the relevant cancers among the female population the aims of this project were to address three main research questions:

- A. What are the temporal trends of SPCs and SIRs among patients diagnosed with a an FPC in 2000-03, 2004-07 and 2008-11 in Northern Portugal;
- B. What is the risk of SPCs or third primary cancers (TPCs) in Northern Portugal, taking into account the competing event of death, among survivors from female breast, endometrial, ovarian and cervical cancer;
- C. What is the contribution of SPCs to the survival of patients diagnosed with a breast FPC in Northern Portugal.

The following specific aims were:

- 1. To describe temporal trends in the incidence rates and SIRs of SPCs among patients with an FPC (PAPER 1).
- 2. To estimate the incidence rates and SIRs, as well as the probability of being diagnosed with an SPC among patients with a breast FPC (PAPER 2).
- 3. To estimate the contribution of SPCs to the mortality of patients with a breast FPC (PAPER 3).

4. To estimate the long-term risk and survival of TPCs among patients with a breast FPC (PAPER 4).
5. To estimate the incidence rates and SIRs, and as well as the probability of being diagnosed with an SPC among patients with a cervical, endometrial, or ovarian FPC (PAPER 5).

METHODS

The objectives of the present thesis were accomplished through the analysis of data from the North Region Cancer Registry (RORENO). This is a population-based cancer registry established in 1988 that covers Northern Portugal, representing over three million residents (90). All incident cancers occurring in the catchment area of the registry are recorded, either by public or private hospitals and clinics, and private pathology laboratories. Registration follows the IARC rules, which includes four dimensions: comparability, validity, timeliness and completeness (91). The quality of the registry is maintained through routine screening with pre-defined algorithms for consistency and validity (91).

To accomplish the research objectives, we used population-based cohorts of patients diagnosed with cancer in the RORENO:

1. A cohort of patients diagnosed with an FPC followed for the occurrence of SPCs and vital status;
2. A cohort of patients diagnosed with a breast FPC followed for the occurrence of SPCs, TPCs and vital status;
3. A cohort of patients diagnosed with a cervical, endometrial, or ovarian FPC followed for the occurrence of SPCs and vital status.

MPCs were defined as proposed by the IACR/IARC (23). The occurrence of any subsequent cancer was ascertained by means of record linkage with the list of cases registered by RORENO until 31 December 2013 or later depending on data availability. Vital status was assessed through the National Health System until 30 June 2021 or later depending on data availability.

The cumulative incidence of SPCs (objectives 2 and 5) and TPCs (objective 4) was estimated considering the competing event of death with follow-up until 31 December 2015, according Kalbfleisch and Prentice method (92).

For objectives 1, 2 and 5, PYAR were calculated from the diagnosis of an FPC until the diagnosis of an SPC, death or end of follow-up, whichever occurred first. The incidence of SPCs was compared with the expected in the general population by calculating SIRs. These were calculated by dividing the observed number of SPCs by the expected number of cases, if the cancer incidence rates in the general

population had been observed among survivors. The latter were estimated by multiplying the cancer incidence in the general population by the PYAR in the corresponding stratum, defined according to sex (objective 1), five-year age group (from 15–19 to 70–74, and ≥ 75 years) and calendar year (objectives 1, 2 and 5). The incidence of cancer among the general Northern Portuguese population, in the corresponding stratum, was acquired from RORENO (92).

To estimate the contribution of SPCs and TPCs to the mortality of FPCs (objectives 3 and 4, respectively), patients diagnosed with an SPC or TPC were matched (1:3, five-year age group and year of FPC diagnosis for objective 3, and 1:1, five-year age group and year of SPC diagnosis for objective 4) to those who did not develop an SPC or a TPC and were alive when the corresponding FPC or SPC was diagnosed, respectively. Cox-proportional hazards regression analyses were used to compute adjusted hazard ratios for all-cause mortality. Cumulative mortality for FPC patients with and without an SPC or TPC diagnosis were calculated using 1-KM (93).

Data analyses were conducted using the statistical program STATA®15.1 (StataCorp, College Station, TX, USA). Results were considered statistically significant for p-value < 0.05 .

The studies were approved by the Ethics Committee of the Portuguese Institute of Oncology of Porto (Ref. CES IPO: 376/017 and 332/020) and the analyses were performed according to RORENO guidelines ensuring the anonymity of information used.

PAPERS

**Temporal trends in the incidence of second primary cancers in
Northern Portugal: a population-based study**

Temporal trends in the incidence of second primary cancers in Northern Portugal: a population-based study

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Short title: Trends in SPCs in Northern Portugal

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Abstract

Background: The number of survivors of cancer is growing. This has led to an increase in the frequency of multiple primary cancers (MPCs). The current study aimed to describe the temporal trends in the incidence rates and standardized incidence ratios (SIRs) of second primary cancers (SPCs) among patients diagnosed with a first primary cancer (FPC) in 2000-03, 2004-07 and 2008-11 in Northern Portugal.

Methods: Population-based samples of patients diagnosed with an FPC (excluding skin non-melanoma) in three periods of four years, between 1/1/2000 and 31/12/2011, and registered in the Portuguese North Region Cancer Registry were followed for the diagnosis of an SPC or death until 31/12/2013. Incidence rates and SIRs were estimated for each period by sex and considering the time between FPC and SPC diagnosis (synchronous and metachronous).

Results: During follow-up, 10119 (7.4%) SPCs were identified among patients diagnosed with an FPC in 2000-11 (n=136382). The incidence rate of SPCs was over 10-fold higher in the first few months, remaining stable over the follow-up. Higher rates were observed in 2004-07 and 2008-11. Overall, a greater proportion of SPCs was diagnosed among males than females. The proportion of SPCs diagnosed increased with age. Increases in SIRs of SPCs were observed from 2000-03 to 2008-11, ranging from 1.16 to 1.77 and from 1.54 to 2.33, among males and females, respectively. This was particularly evident for FPCs and SPCs of the lip, oral cavity, pharynx, oesophagus and larynx among males, and colon and rectum, lung, ovary, and cervix among females.

Conclusion: Survivors of cancer in Northern Portugal had higher incidence rates of cancer than the general population, which have increased over time.

Keywords: Epidemiology, Cancer survivors, Population-based cancer registry, Second primary cancer

Introduction

The number of cancer survivors is growing, reflecting an increase in the overall number of cases of cancer and improvements in prognosis, as a result of early diagnosis and treatment advances, as well as an increase in overall life expectancy (1). This has led to an increase in the frequency of multiple primary cancers (MPCs) (2-4).

Recent estimates show that MPCs account for a considerable proportion of all incident cancers diagnosed (4, 5). A systematic review showed that the incidence of MPCs has increased in the USA and Australia (3). In particular, the proportion of MPCs doubled from 9.8% for cancers diagnosed between 1975–1984 to 21.0% between 2015–2017 in the USA (4). However, trends in MPCs vary according to the region and period studied (3). Factors such as the definition of MPCs, study follow-up time and differences between regions in terms of standard of care delivered or environmental exposures may influence trends (5, 6). Individuals may be more susceptible to MPCs due to a variety of factors, namely persisting effects of environmental exposures or genetic susceptibility, which also contribute for the occurrence of first primary cancers (FPCs), as well as improvements in medical imaging and increased use of screening programs, greater medical surveillance during cancer diagnosis and follow-up, and long-term side-effects of cancer treatment (2, 4, 5, 7, 8).

The study of temporal trends is fundamental for anticipating the impact of MPCs in patients with a previous cancer and to define priorities around survivorship care (9). Therefore, the current study aims to describe temporal trends in the incidence rates and standardized incidence rates (SIRs) of second primary cancers (SPCs) among FPCs diagnosed in 2000–03, 2004–07 and 2008–11 in Northern Portugal.

Methods

Study setting

Cancer data were obtained from the North Region Cancer Registry (RORENO), a population-based cancer registry established in 1988 that covers the entire Northern region of Portugal, corresponding to 3.3 million inhabitants (10). All new diagnoses from public or private clinics in the North of the country are included. The registry follows the cancer registration principles of the International Agency for Research on Cancer (IARC) (11).

Tumor classification and definition of second primary cancers

Tumour topography and morphology were classified according to the International Classification of Diseases for Oncology, Third Edition (12) and recoded according to the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (13). MPCs were defined following the guidelines of the International Association of Cancer Registries and IARC (14). Briefly, MPCs are defined as two or more unrelated tumours, irrespective of the time that they originally developed in an organ or a tissue, not being an extension, a recurrence, or a metastasis, and have different morphologies (even with the same topography) and topographies.

Study design

The study cohort included all adult Northern Portuguese residents diagnosed with an FPC (excluding skin non-melanoma) between 1/1/2000 and 31/12/2011. Vital status to 31/12/2013 was assessed through record linkage with the National Health System database. The diagnosis of any SPC to 31/12/2013 was ascertained through linkage with cases registered by RORENO. SPCs were classified as synchronous when diagnosed simultaneously or within two months, or metachronous otherwise. Third and subsequent primaries were excluded from the present analysis.

Statistical analysis

Patient characteristics were presented as counts and proportions for categorical variables, and median (percentile 25-percentile 75) for continuous variables. Median follow-up time was estimated using the reverse Kaplan-Meier (15). The median follow-up time among patients with a metachronous SPC ranged from nearly five years for patients diagnosed with an FPC in 2000–03 to 1.47 years among patients with an FPC in 2008–11. Analyses were carried out for all, synchronous and metachronous SPCs, and stratified by sex and period of FPC diagnosis (2000–03, 2004–07, 2008–11).

Person-years at risk (PYAR) were calculated as the time from FPC to SPC diagnosis, death, or end of follow-up (31/12/2013), whichever occurred first. The incidence rates of SPCs by period of FPC diagnosis (2000–03, 2004–07, 2008–11) by sex were computed by dividing the number of incident SPCs by the PYAR within each interval and represented in the respective midpoint of the interval: 0 to <1 month, ≥1 to <2 months, ≥2 to <3 months, ≥3 to <4 months, ≥4 to <5 months, ≥5 to <6 months, ≥6 to <7 months, ≥7 to <8 months, ≥8 to <9 months, ≥9 to <10 months, ≥10 to <11 months, ≥11 to <12 months, and then for each six months of follow-up until 72 months.

The incidence of SPCs was compared with age-, sex- and calendar year-specific rates in the general population from Northern Portugal, by calculating SIRs for each period of FPC diagnosis (2000–03, 2004–07, 2008–11) with follow-up to 31/12/2013. SIRs were calculated by dividing the observed number of SPCs by the expected number of cancer cases in the same time period, if the cancer incidence rates in the general population had been observed among cancer survivors. The expected number of cancer cases was estimated by multiplying the PYAR among survivors of cancer by the corresponding sex, five-year age group (from 15–19 to 70–74, and ≥75) and calendar year cancer incidence rates observed in the general population of Northern Portugal. The cancer incidence among the general Northern region Portuguese population was obtained from RORENO (10). The 95%

confidence intervals (CIs) were estimated assuming a *Poisson* probability distribution. SIRs and the corresponding 95%CIs were estimated for all, synchronous and metachronous SPCs separately.

Statistical analyses were performed using STATA®15.1 (StataCorp, College Station, TX, USA). Results were considered statistically significant for p-values<0.05.

Results

During follow-up, 10119 (7.4%) SPCs were identified among 136382 patients with an FPC diagnosed between 2000 and 2011, of which 2525 (24.9%) were diagnosed within two months of the FPC (**Table 1**). Over half of all patients diagnosed with an FPC between 2000 and 2011 were male (54.6%), with SPCs being more frequent among males (61.7%). The median age at FPC diagnosis for patients with and without an SPC ranged between 64 and 68 years. The proportion of SPCs diagnosed generally increased with age. SPCs occurred most frequently among patients with an FPC of the colon and rectum (n=2258), prostate (n=1451), and breast (n=1083). The most common SPCs occurred in the colon and rectum (n=2310), lung (n=1180), and prostate (n=832).

The incidence rate of SPCs was over 10-fold higher in the first two months of follow-up than in the remaining follow-up period with higher incidence rates being observed among patients diagnosed with an FPC more recently (2004–07 and 2008–11). Incidence rates reached 24000/100000 person-years in males and 17000/100000 person-years among females in the first month following an FPC diagnosis in 2008–11, being approximately 10000/100000 in males and females diagnosed with an FPC in 2000–03. Incidence rates remained relatively stable from four months on and were similar when considering the period of FPC diagnosis (**Figure 1**).

Table 2 shows the SIRs for SPCs among patients with an FPC diagnosed in the periods analysed. Considering all FPCs, the SIRs (95%CI) for an SPC increased from 1.16 (1.11-1.21) among males with an FPC in 2000–03 to 1.77 (1.69-1.85) for those with an FPC in 2008–11, and from 1.54 (1.46-1.63) to 2.33 (2.20-2.46) for females with an FPC in the corresponding years. Likewise, the SIRs for metachronous SPCs increased from 1.02 (0.97-1.07) for males with an FPC in 2000–03 to 1.22 (1.15-1.28) for those with an FPC in 2008–11, and from 1.29 (1.21-1.37) to 1.51 (1.40-1.62) for females with an FPC in the corresponding years.

Stratified analyses by FPC sites also showed that SIRs generally increased for patients diagnosed with an FPC from 2000–03 to 2008–11. The highest SIRs for all SPCs among males were observed for FPC sites of the lip, oral cavity, and pharynx (SIRs ranging from 1.96 for males with an FPC in 2000–03 to 5.51 for patients diagnosed in 2008–11), oesophagus (SIRs ranging from 2.82 to 4.14), and larynx (SIRs ranging from 2.34 to 3.91). The lowest SIRs for all SPCs among males were observed for FPC sites of the stomach (SIRs ranging from 1.29 to 1.73), and colon and rectum (SIRs ranging from 1.27 to 2.43). Males diagnosed with an FPC of the prostate had a lower incidence of cancer overall compared to males from the general population, though a higher incidence within the first two months of the FPC.

The highest SIRs for all SPCs among females were observed for FPC sites of the colon and rectum (SIRs ranging from 1.82 for females with an FPC in 2000–03 to 3.87 for patients diagnosed in 2008–11), lung (SIRs ranging from 3.71 to 2.99), and ovary (SIRs ranging from 1.92 to 4.41). The lowest SIRs for all SPCs among females were observed for FPC sites of the stomach (SIRs ranging from 1.32 to 2.04), bladder (SIRs ranging from 1.04 to 1.70), and thyroid (SIRs ranging from 1.06 to 1.59). Females with an FPC, regardless of the site, had a higher incidence of cancer compared to females from the general population.

Table 3 shows the SIRs for selected SPC sites diagnosed among all patients with an FPC in 2000–03, 2004–07, and 2008–11. Cancers of the lip, oral cavity, and pharynx (SIRs ranging from 1.83 for males with an FPC in 2000–03 to 3.81 for patients diagnosed in 2008–11), oesophagus (SIRs ranging from 1.70 to 3.04), and larynx (SIRs ranging from 1.55 to 3.19) had the highest SIRs among males diagnosed with an FPC compared to males from the general population. Contrarily, males diagnosed with an FPC had a lower incidence of prostate cancer (SIRs ranging from 0.63 to 0.89) compared to males from the general population.

Generally, females diagnosed with an FPC had a higher incidence of cancers compared to the general female population. The highest SIRs were observed for SPCs of the colon and rectum (SIRs ranging

from 2.49 for females with an FPC in 2000–03 to 2.41 for patients diagnosed in 2008–11), cervix uteri (SIRs ranging from 1.89 to 3.18), and ovary (SIRs ranging from 2.24 to 4.00). The lowest SIRs were observed for SPCs of the stomach (SIRs ranging from 1.27 to 1.71), breast (1.11 to 1.66), and non-Hodgkin lymphoma (SIRs ranging from 1.13 to 2.15).

Discussion

In Northern Portugal, the incidence rates, and SIRs of SPCs increased overtime among patients with an FPC diagnosed between 2000 and 2011 with a follow-up to the end of 2013. Generally, both males and females had a higher incidence of SPCs compared to the general population. Specifically, the highest SIRs for SPCs were observed among male survivors of lip, oral cavity and pharynx, oesophagus, and larynx cancers, and female survivors of the colon and rectum, lung, and ovary. The highest SIRs were observed for SPCs of the lip, oral cavity, and pharynx, oesophagus, and larynx among males and of the colon and rectum, cervix uteri, and ovary among females.

A systematic review on the temporal trends of MPCs by Ye and colleagues yielded contradictory results (3). A study from Australia found that SIRs for any SPC increased from 1.14 to 1.46 for patients with a first cancer diagnosis between 1980 through 1984, and 2005 through 2009 with follow up to December 2013 (6). In Europe, SIRs for SPCs have remained stable from 1978 to 2010 in Italy during a mean follow-up time of 14 years (16), while no significant changes were observed for patients diagnosed with a first cancer between 1989 and 2004, and followed up until December 31, 2004, in France (17). In the current study, which considered patients with a previous cancer diagnosed in three periods between 2000 and 2011 with a follow-up to the end of 2013, we found higher incidence rates and SIRs of SPCs among patients diagnosed with FPCs more recently, both for synchronous and metachronous SPCs. Moreover, as expected, the proportion of SPCs among patients followed for a longer time was higher.

The variations in trends of SPCs observed may be explained by the definition used to classify SPCs in terms of terminology, as well as the cut-off used to define synchronous and metachronous tumours. Two coding rules have been used internationally to define MPCs: the Surveillance Epidemiology and End Results (SEER) Program (18), used mainly by North American cancer registries, and the IACR/IARC definition (14), which was used in our study. Tumor site and histology are fundamental in both for

defining subsequent primary cancers. Generally, the definition of subsequent primary cancer by SEER are more complex and may yield more MPCs than using the IACR/IARC definition (5, 19-21). Moreover, the time cut-off used to define synchronous and metachronous tumours among studies yield different numbers of SPCs in each group (2, 3). The current study used two-months as the cut-off between FPCs and SPCs to define synchronous and metachronous tumours, which has been used in previous research (4, 22-24). Cut-offs such as six and 12 months have also been used to define tumours as synchronous and metachronous (5, 25-27).

In the current study, we have shorter follow-up times for patients diagnosed in the most recent periods, leading synchronous SPCs to have a greater weight in the calculated rates (they are less diluted). Nevertheless, the rising incidence rates of SPCs observed here and in previous research may be a result of use of increasingly sensitive imaging tests in routine clinical follow-ups for survivors of cancer. However, early detection and incidental findings may potentially lead to the "overdiagnosis" of subsequent primary cancers among patients with a previous cancer (28). In the review by Ye and colleagues, a higher incidence of MPCs was observed in studies from the USA and Australia in the late 1990s, which may be related with the introduction of national cancer screening programs (3). Moreover, Corkum and colleagues reported that survivors of cancer were more likely to receive cancer screening for new primary cancers (28). In Northern Portugal, organized screening for breast and cervical cancers were implemented in 2009 (29), which may have affected the last period of analysis (2008-2011). Colorectal cancer screening was introduced in 2016 (30), which is after the period of FPC and SPC diagnoses considered in our study. Furthermore, a recent national population-based cross-sectional study reported that annual screening for breast, cervical and prostate cancers were more frequent among individuals with a previous cancer diagnosis (31).

The rising incidence of cancer may also be attributed to increased use of medical imaging and advancements in computerized tomography scanning, leading to incidental findings during cancer staging and follow-up (32). There has been a global increase in radiation exposure from medical

radiological procedures, in recent decades (33). Diagnostic X-rays contribute to a lifetime cancer risk, while CT scanning, widely used since the 1990s, poses a higher radiation dose, which may lead to an overall increased cancer risk among the general population as well as survivors of cancer (33). Moreover, the introduction of newer and improved cancer treatments, namely chemotherapy and radiotherapy, have improved prognosis, allowing survivors to live longer and potentially develop MPCs (6, 34, 35). Healthcare system standards, encompassing access to primary care, screenings, advanced imaging, and treatments, also play a role in the incidence of MPCs (4, 5, 7). In Portugal, universal and tax-free medical care for patients with cancer follows high-standard protocols (36).

Changing lifestyle or environmental risk factors may have also influenced the temporal trends in the incidence of SPCs. Variations in population exposure to carcinogenic factors, such as alcohol consumption and tobacco smoking, across countries may contribute to the differences observed (37). In our study, we found the highest SIRs in tobacco-related cancer sites among males, namely lip, oral cavity, and pharynx, oesophagus, and larynx. Previous research has shown the synergic effect of alcohol and tobacco contributes to certain cancer site combinations (22, 38). A previous systematic review in Northern Portugal found that the prevalence of tobacco smoking decreased for males between 1987 and 2008, while it increased for females in the same period. On the other hand, the prevalence of alcohol drinking increased slightly among males and decreased among females (39). Nevertheless, we must also consider the lag times between exposure and outcome, which may vary from as little as five years to 20 years or more depending on exposure-outcome pair considered (39). In addition, the highest SIRs for females were for cancer sites of the colon and rectum, lung, ovary, and cervix. Previous studies have also shown that the incidence of some of these cancers is influenced by hormonal factors, the environment and diet (7, 40).

Despite the strength from a population-based cancer registry used in our study, some limitations need to be pointed. Although the proportion of SPCs is expected to increase with greater registry operating time (41), RORENO was established in 1988, and only FPCs diagnosed in 2000-11 were considered in

our study. Additionally, the incidence rates used to calculate SIRs were obtained from the general population of the registry's catchment area. As such, we expect that the completeness of the registry regarding both FPCs and MPCs will have a negligible impact on the increased SIRs observed. Our study lacked information on tumor staging at diagnosis, lifestyle and dietary characteristics, genetic status and oncological treatments received, which was not available. Previous studies have shown that certain lifestyle characteristics, such as persistent tobacco smoking, are related to specific cancers (42), genetic susceptibility is an important factor for carcinogenesis (7, 43), and cancer treatments play an important role in MPCs (43).

In conclusion, cancer survivors had higher incident rates of cancer than the general population, which have increased over time. These findings have clinical implications on surveillance of patients with cancer, on their expectations and eventual economic burden. Identifying risk factors and patterns of cancer site diagnoses could help implementing strategies, such as counselling and screening among this growing population.

Statements

Acknowledgments: None.

Ethics

Ethical approval: The study was approved by the Ethics Committee of the Portuguese Institute of Oncology of Porto (Ref. CES IPO: 376/017) and the analyses were performed according to RORENO guidelines for pseudo anonymization of information used. All procedures performed were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Ethical Review Board: The Ethics Committee of the Portuguese Institute of Oncology of Porto (Ref. CES IPO: 376/017) approved the study protocol.

Informed consent: The study was granted an exemption from requiring written informed consent by the Ethics Committee of the Portuguese Institute of Oncology of Porto (Ref. CES IPO: 376/017).

Conflicts of interest: None.

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Author contributions: EG was responsible for writing – original draft. EG and SM were responsible formal analysis, investigation, and methodology. SM and NL conceptualized and visualized the study. SM supervised the study. All authors were responsible for data curation and writing – review and editing.

Data availability statement: The data that support the findings of this study are available from North Region Cancer Registry of Portugal (RORENO), but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of RORENO.

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Table 1. Characteristics of cancer patients with synchronous and metachronous second primary cancers (follow-up to the end of 2013) according to calendar year of first primary cancer diagnosis (2000–03, 2004–07, 2008–11).

	Calendar year of first primary cancer diagnosis								
	2000–03			2004–07			2008–11		
	Without an SPC	With an SPC		Without an SPC	With an SPC		Without an SPC	With an SPC	
N	N=34244 (91.5%)	N=3173 (8.5%)		N=41995 (91.9%)	N=3695 (8.1%)		N=50024 (93.9%)	N=3251 (6.1%)	
Sex (N [%])		Synchronous 501	Metachronous 2672		Synchronous 833	Metachronous 2862		Synchronous 1191	Metachronous 2060
Males	18533 (54.1)	275 (54.9)	1641 (61.4)	23012 (54.8)	484 (58.1)	1845 (64.5)	26655 (53.3)	705 (59.2)	1292 (62.7)
Females	15711 (45.9)	226 (45.1)	1031 (38.6)	18983 (45.2)	349 (41.9)	1017 (35.5)	23369 (46.7)	486 (40.8)	768 (37.3)
Age at FPC diagnosis, years									
Median (P25-P75)	65 (53-74)	64 (53-73)	66 (57-72)	65 (53-74)	65 (55-74)	67 (58-73)	65 (54-75)	65 (53-74)	68 (59-75)
<45	4400 (12.9)	58 (11.6)	176 (6.6)	5069 (12.1)	70 (8.4)	172 (6.0)	5563 (11.1)	86 (7.2)	100 (4.8)
45-54	5220 (15.3)	82 (16.4)	370 (13.8)	6511 (15.5)	137 (16.4)	363 (12.7)	7458 (14.9)	209 (17.6)	217 (10.5)
55-64	7137 (20.9)	110 (22.0)	685 (25.6)	9073 (21.6)	193 (23.2)	685 (23.9)	11595 (23.2)	294 (24.6)	498 (24.2)
65-74	9811 (28.7)	154 (30.7)	1026 (38.4)	11555 (27.5)	228 (27.4)	1036 (36.2)	12839 (25.7)	318 (26.7)	726 (35.2)
≥75	7644 (22.3)	97 (19.4)	415 (15.5)	9784 (23.3)	205 (24.6)	606 (21.2)	12554 (25.1)	284 (23.9)	519 (25.2)
FPC site (N [%]) ^a									
Lip, oral cavity and pharynx	1110 (3.2)	32 (6.9)	102 (3.8)	1324 (3.1)	74 (8.9)	136 (4.7)	1513 (3.0)	97 (8.1)	108 (5.2)
Oesophagus	623 (1.8)	23 (4.6)	19 (0.7)	607 (1.4)	14 (1.7)	36 (1.3)	672 (1.3)	27 (2.3)	21 (1.0)
Stomach	3906 (11.4)	39 (7.8)	179 (6.7)	4155 (9.9)	51 (6.1)	162 (5.7)	4331 (8.7)	81 (6.8)	118 (5.7)
Colon and rectum	5176 (15.1)	120 (23.9)	489 (18.3)	6235 (14.9)	247 (29.6)	550 (19.2)	7619 (15.2)	389 (32.7)	463 (22.5)
Larynx	497 (1.4)	16 (3.2)	72 (2.7)	489 (1.2)	28 (3.4)	85 (3.0)	579 (1.2)	34 (2.8)	57 (2.8)
Trachea, bronchus and lung	2867 (8.4)	52 (10.3)	68 (2.5)	3689 (8.8)	67 (8.0)	81 (2.8)	4222 (8.4)	91 (7.6)	77 (3.7)
Breast	4458 (13.0)	53 (10.6)	336 (12.6)	5505 (13.1)	81 (9.7)	294 (10.3)	6828 (13.6)	115 (9.6)	204 (9.9)
Cervix uteri	838 (2.4)	13 (2.6)	61 (2.3)	773 (1.8)	16 (1.9)	46 (1.6)	786 (1.6)	28 (2.3)	24 (1.2)
Corpus uteri	599 (1.7)	11 (2.2)	55 (2.1)	740 (1.8)	25 (3.0)	52 (1.8)	998 (2.0)	32 (2.7)	53 (2.6)
Ovary	368 (1.1)	9 (1.8)	20 (0.7)	390 (0.9)	11 (1.3)	25 (0.9)	432 (0.9)	13 (1.1)	22 (1.1)
Prostate	3986 (11.6)	28 (5.6)	505 (18.9)	5426 (12.9)	44 (5.3)	548 (19.1)	6113 (12.2)	35 (2.9)	291 (14.1)
Kidney	558 (1.6)	14 (2.8)	64 (2.4)	694 (1.6)	18 (2.2)	80 (2.8)	989 (2.0)	12 (1.0)	64 (3.1)
Bladder	1615 (4.7)	22 (4.4)	238 (8.9)	1965 (4.7)	28 (3.4)	256 (8.9)	2205 (4.4)	61 (5.1)	181 (8.8)
Thyroid	1148 (3.4)	5 (1.0)	87 (3.3)	1912 (4.5)	18 (2.2)	79 (2.8)	2727 (5.4)	19 (1.6)	70 (3.4)
Non-Hodgkin lymphoma	1033 (3.0)	9 (1.8)	80 (3.0)	1370 (3.3)	9 (1.1)	91 (3.2)	1588 (3.2)	20 (1.7)	66 (3.2)
SPC site (N [%]) ^a									
Lip, oral cavity and pharynx	--	31 (6.2)	84 (3.1)	--	65 (7.8)	126 (4.4)	--	89 (7.5)	75 (3.6)
Oesophagus	--	10 (2.0)	52 (1.9)	--	10 (1.2)	57 (2.0)	--	26 (2.2)	38 (1.8)
Stomach	--	37 (7.4)	233 (8.7)	--	57 (6.8)	182 (6.4)	--	71 (6.0)	141 (6.8)
Colon and rectum	--	118 (23.5)	545 (20.4)	--	272 (32.6)	592 (20.7)	--	374 (31.4)	409 (19.8)
Larynx	--	14 (2.8)	33 (1.2)	--	30 (3.6)	45 (1.6)	--	32 (2.7)	29 (1.4)
Trachea, bronchus and lung	--	57 (11.4)	336 (12.6)	--	72 (8.6)	346 (12.1)	--	117 (9.8)	252 (12.2)
Breast	--	53 (10.6)	178 (6.7)	--	82 (9.8)	179 (6.2)	--	105 (8.8)	132 (6.4)

Cervix uteri	--	13 (2.6)	35 (1.3)	--	9 (1.1)	28 (1.0)	--	20 (1.7)	21 (1.0)
Corpus uteri	--	12 (2.4)	64 (2.4)	--	25 (3.0)	48 (1.7)	--	30 (2.5)	27 (1.3)
Ovary	--	11 (2.2)	24 (0.9)	--	10 (1.2)	23 (0.8)	--	19 (1.6)	19 (0.9)
Prostate	--	23 (4.6)	251 (9.4)	--	27 (3.4)	282 (9.5)	--	48 (4.0)	201 (9.8)
Kidney	--	13 (2.6)	69 (2.6)	--	28 (3.4)	95 (3.3)	--	37 (3.1)	57 (2.8)
Bladder	--	26 (5.2)	164 (6.1)	--	34 (4.1)	195 (6.8)	--	21 (1.8)	118 (5.7)
Thyroid gland	--	6 (1.2)	61 (2.3)	--	8 (1.0)	81 (2.8)	--	12 (1.0)	74 (3.6)
Non-Hodgkin lymphoma	--	12 (2.4)	72 (2.7)	--	8 (1.0)	79 (2.8)	--	24 (2.0)	63 (3.1)
Follow-up, years (median [P25-P75]) ^b	11.8 (10.9-12.8)	0.1 (0.0-0.1)	4.9 (2.0-8.0)	7.9 (6.9-8.9)	0.1 (0.0-0.0)	3.1 (1.3-5.3)	3.9 (2.9-4.9)	0.1 (0.0-0.1)	1.5 (0.5-2.6)
Dead (N [%]) ^c	21414 (62.5)	381 (76.0)	1650 (61.8)	21738 (51.8)	538 (64.6)	1560 (54.5)	19816 (39.6)	630 (52.9)	847 (41.1)

Note: In each variable, the total may not add up due to missing data. FPC – First Primary Cancer; P25 – percentile 25, P75 percentile 75, SPC – Second Primary Cancer.

^a Lip, oral cavity and pharynx (C00–C14), Oesophagus (C15), Stomach (C16), Colon and rectum (C18–C20), Larynx (C32), Trachea, bronchi and lung (C33–C34), Female breast (C50), Cervix uteri (C53), Corpus uteri (C54), Ovary (C56), Prostate (C61), Kidney (C64), Bladder (C67), Thyroid (C73), Non-Hodgkin Lymphoma (C82–86, C96) defined according to the International Statistical Classification of Diseases and Related Health Problems, 10th Revision.

^b Follow-up to 31 December 2013 until SPC, death or end of follow-up. Median follow-up time was estimated using the reverse Kaplan-Meier.

^c Follow-up to 31 December 2013.

Table 2. Standardized incidence ratios for all second primary cancers among selected first primary cancers (follow-up to 31 December 2013) by calendar year of first primary cancer diagnosis (2000–03, 2004–07, 2008–11) among males and females.

	First primary cancer site ^a	Calendar year of first primary cancer diagnosis	All second primary cancers			Synchronous second primary cancers			Metachronous second primary cancers		
			Expected	Observed	SIR (95%CI)	Expected	Observed	SIR (95%CI)	Expected	Observed	SIR (95%CI)
MALES	ALL	2000-03	1656	1916	1.16 (1.11-1.21)	42	275	6.6 (5.85-7.43)	1614	1641	1.02 (0.97-1.07)
		2004-07	1702	2329	1.37 (1.31-1.43)	57	484	8.52 (7.78-9.31)	1645	1845	1.12 (1.07-1.17)
		2008-11	1131	1997	1.77 (1.69-1.85)	68	705	10.38 (9.62-11.17)	1063	1292	1.22 (1.15-1.28)
	LIP, ORAL CAVITY AND PHARYNX	2000-03	55	107	1.96 (1.61-2.37)	2	25	16.09 (10.41-23.76)	53	82	1.55 (1.23-1.92)
		2004-07	48	180	3.72 (3.19-4.3)	2	66	34.32 (26.55-43.67)	47	114	2.45 (2.02-2.94)
		2008-11	32	174	5.51 (4.72-6.39)	2	85	38.84 (31.02-48.03)	29	89	3.03 (2.43-3.72)
	OESOPHAGUS	2000-03	11	32	2.82 (1.93-3.98)	1	17	19.51 (11.36-31.24)	10	15	1.43 (0.8-2.36)
		2004-07	13	42	3.27 (2.35-4.42)	1	11	10.78 (5.38-19.3)	12	31	2.62 (1.78-3.72)
		2008-11	9	38	4.14 (2.93-5.68)	1	20	19.04 (11.63-29.41)	8	18	2.21 (1.31-3.5)
	STOMACH	2000-03	113	146	1.29 (1.09-1.51)	5	21	4.26 (2.64-6.51)	108	125	1.15 (0.96-1.37)
		2004-07	103	135	1.31 (1.1-1.56)	6	31	5.52 (3.75-7.84)	97	104	1.07 (0.87-1.3)
		2008-11	75	130	1.73 (1.44-2.05)	6	58	9.27 (7.04-11.99)	69	72	1.04 (0.82-1.31)
	COLON AND RECTUM	2000-03	295	375	1.27 (1.15-1.41)	7	69	9.93 (7.73-12.57)	288	306	1.06 (0.95-1.19)
		2004-07	300	480	1.6 (1.46-1.75)	10	146	15.06 (12.72-17.71)	290	334	1.15 (1.03-1.28)
		2008-11	226	520	2.3 (2.11-2.51)	13	225	17.94 (15.68-20.45)	213	295	1.38 (1.23-1.55)
	LARYNX	2000-03	36	87	2.43 (1.94-2.99)	1	15	16.29 (9.12-26.86)	35	72	2.06 (1.61-2.59)
		2004-07	27	108	4.05 (3.32-4.89)	1	27	27.15 (17.9-39.51)	26	81	3.15 (2.51-3.92)
		2008-11	23	90	3.91 (3.14-4.8)	1	33	26.6 (18.31-37.36)	22	57	2.62 (1.98-3.39)
	TRACHEA, BRONCHI AND LUNG	2000-03	47	91	1.94 (1.56-2.39)	4	38	8.49 (6.01-11.66)	42	53	1.25 (0.94-1.64)
		2004-07	62	121	1.95 (1.62-2.33)	6	48	7.99 (5.89-10.59)	56	73	1.3 (1.02-1.63)
		2008-11	59	130	2.22 (1.86-2.64)	7	73	9.88 (7.74-12.42)	51	57	1.11 (0.84-1.44)
	PROSTATE	2000-03	706	533	0.75 (0.69-0.82)	12	28	2.35 (1.56-3.4)	695	505	0.73 (0.67-0.79)
		2004-07	747	592	0.79 (0.73-0.86)	17	44	2.53 (1.83-3.39)	730	548	0.75 (0.69-0.82)

FEMALES	KIDNEY	2008-11	427	326	0.76 (0.68-0.85)	19	35	1.82 (1.27-2.53)	407	291	0.71 (0.63-0.8)
		2000-03	40	55	1.38 (1.04-1.8)	0	11	23.96 (11.96-42.87)	39	44	1.12 (0.81-1.5)
		2004-07	36	75	2.08 (1.63-2.6)	1	15	15.13 (8.47-24.95)	35	60	1.71 (1.3-2.2)
		2008-11	30	64	2.16 (1.66-2.76)	1	11	7.36 (3.67-13.17)	28	53	1.88 (1.41-2.46)
	BLADDER	2000-03	160	228	1.42 (1.25-1.62)	3	20	6.04 (3.69-9.33)	157	208	1.33 (1.15-1.52)
		2004-07	159	254	1.6 (1.41-1.81)	5	25	5.27 (3.41-7.78)	154	229	1.49 (1.3-1.69)
		2008-11	97	216	2.23 (1.94-2.55)	5	56	10.69 (8.08-13.88)	92	160	1.75 (1.49-2.04)
	NON-HODGKIN LYMPHOMA	2000-03	36	55	1.53 (1.15-1.99)	1	5	5.3 (1.72-12.38)	35	50	1.43 (1.06-1.88)
		2004-07	44	59	1.34 (1.02-1.73)	1	5	3.36 (1.09-7.84)	43	54	1.27 (0.95-1.66)
		2008-11	28	55	1.96 (1.47-2.55)	2	14	7.91 (4.32-13.26)	26	41	1.56 (1.12-2.11)
	ALL	2000-03	814	1257	1.54 (1.46-1.63)	16	226	13.99 (12.22-15.94)	798	1031	1.29 (1.21-1.37)
		2004-07	754	1336	1.77 (1.68-1.87)	21	319	15.03 (13.42-16.77)	732	1017	1.39 (1.3-1.48)
		2008-11	538	1254	2.33 (2.2-2.46)	30	486	16.45 (15.02-17.98)	509	768	1.51 (1.4-1.62)
	STOMACH	2000-03	54	72	1.34 (1.05-1.69)	2	18	10.16 (6.02-16.05)	52	54	1.04 (0.78-1.36)
		2004-07	48	78	1.63 (1.29-2.04)	2	20	9.53 (5.82-14.72)	46	58	1.27 (0.96-1.64)
		2008-11	34	69	2.04 (1.59-2.58)	3	23	8.87 (5.62-13.31)	31	46	1.47 (1.08-1.96)
	COLON AND RECTUM	2000-03	129	234	1.82 (1.59-2.07)	3	51	17.52 (13.05-23.04)	126	183	1.45 (1.25-1.68)
		2004-07	123	317	2.59 (2.31-2.89)	4	101	26.43 (21.53-32.11)	119	216	1.82 (1.58-2.08)
		2008-11	86	332	3.87 (3.46-4.31)	5	164	33.15 (28.27-38.63)	81	168	2.08 (1.78-2.42)
	TRACHEA, BRONCHI AND LUNG	2000-03	8	29	3.71 (2.48-5.33)	1	14	27.32 (14.94-45.84)	7	15	2.05 (1.15-3.39)
		2004-07	11	27	2.47 (1.63-3.6)	1	19	25.09 (15.11-39.18)	10	8	0.79 (0.34-1.55)
		2008-11	13	38	2.99 (2.12-4.1)	1	18	14.3 (8.47-22.6)	11	20	1.75 (1.07-2.7)
	BREAST	2000-03	303	389	1.28 (1.16-1.42)	4	53	12.29 (9.21-16.08)	299	336	1.13 (1.01-1.25)
		2004-07	271	375	1.39 (1.25-1.53)	6	81	13.99 (11.11-17.39)	265	294	1.11 (0.99-1.24)
		2008-11	181	319	1.76 (1.57-1.97)	8	115	14.35 (11.85-17.23)	173	204	1.18 (1.02-1.35)
	CERVIX UTERI	2000-03	39	74	1.9 (1.49-2.39)	1	13	18.66 (9.93-31.9)	38	61	1.6 (1.22-2.05)
		2004-07	26	62	2.35 (1.8-3.01)	1	16	23.06 (13.18-37.45)	26	46	1.79 (1.31-2.38)
		2008-11	15	52	3.54 (2.65-4.65)	1	28	36.19 (24.05-52.3)	14	24	1.73 (1.11-2.57)
	CORPUS UTERI	2000-03	41	66	1.59 (1.23-2.03)	1	11	12.83 (6.4-22.96)	41	55	1.36 (1.02-1.77)
		2004-07	39	77	1.97 (1.55-2.46)	1	25	25.44 (16.46-37.55)	38	52	1.36 (1.02-1.79)

OVARY	2008-11	30	85	2.85 (2.27-3.52)	1	32	21.43 (14.66-30.25)	28	53	1.87 (1.4-2.44)
	2000-03	15	29	1.92 (1.29-2.76)	0	9	26.91 (12.31-51.09)	15	20	1.36 (0.83-2.1)
	2004-07	12	36	2.97 (2.08-4.11)	0	11	26.53 (13.24-47.46)	12	25	2.13 (1.38-3.15)
	2008-11	8	35	4.41 (3.07-6.13)	1	13	24.97 (13.3-42.7)	7	22	2.96 (1.86-4.49)
BLADDER	2000-03	31	32	1.04 (0.71-1.47)	1	2	3.6 (0.44-13)	30	30	1 (0.67-1.42)
	2004-07	22	30	1.38 (0.93-1.97)	1	3	4.83 (1-14.12)	21	27	1.28 (0.84-1.86)
	2008-11	15	26	1.7 (1.11-2.49)	1	5	5.81 (1.89-13.55)	14	21	1.46 (0.9-2.23)
	2000-03	58	76	1.31 (1.03-1.64)	1	5	7.69 (2.5-17.94)	57	71	1.24 (0.97-1.56)
THYROID	2004-07	65	69	1.06 (0.82-1.34)	1	11	9.24 (4.61-16.54)	64	58	0.9 (0.69-1.17)
	2008-11	50	55	1.1 (0.83-1.43)	2	8	3.96 (1.71-7.8)	48	47	0.98 (0.72-1.3)
	2000-03	21	34	1.59 (1.1-2.22)	1	4	7.91 (2.16-20.26)	21	30	1.43 (0.97-2.05)
	2004-07	23	41	1.79 (1.29-2.43)	1	4	5.34 (1.45-13.67)	22	37	1.67 (1.18-2.31)
NON-HODGKIN LYMPHOMA	2008-11	18	31	1.75 (1.19-2.48)	1	6	6.01 (2.21-13.09)	17	25	1.49 (0.96-2.2)

SIR – Standardized Incidence Ratios, SPC – Second Primary Cancer, 95% CI – 95% Confidence Interval.

^a Lip, oral cavity and pharynx (C00–C14), Oesophagus (C15), Stomach (C16), Colon and rectum (C18–C20), Larynx (C32), Trachea, bronchi and lung (C33–C34), Female breast (C50), Cervix uteri (C53), Corpus uteri (C54), Ovary (C56), Prostate (C61), Kidney (C64), Bladder (C67), Thyroid (C73), Non-Hodgkin Lymphoma (C82–86, C96) defined according to the International Statistical Classification of Diseases and Related Health Problems, 10th Revision.

Table 3. Standardized incidence ratios for selected second primary cancers among all first primary cancers (follow-up to 31 December 2013) by calendar year of first primary cancer diagnosis (2000–03, 2004–07, 2008–11) among males and females.

	Second primary cancer site	Calendar year of first primary cancer diagnosis	All second primary cancers			Synchronous second primary cancers			Metachronous second primary cancers		
			Expected	Observed	SIR (95%CI)	Expected	Observed	SIR (95%CI)	Expected	Observed	SIR (95%CI)
MALES	ALL	2000-03	1656	1916	1.16 (1.11-1.21)	42	275	6.6 (5.85-7.43)	1614	1641	1.02 (0.97-1.07)
		2004-07	1702	2329	1.37 (1.31-1.43)	57	484	8.52 (7.78-9.31)	1645	1845	1.12 (1.07-1.17)
		2008-11	1131	1997	1.77 (1.69-1.85)	68	705	10.38 (9.62-11.17)	1063	1292	1.22 (1.15-1.28)
	LIP, ORAL CAVITY AND PHARYNX	2000-03	52	95	1.83 (1.48-2.24)	1	26	17.73 (11.58-25.98)	50	69	1.37 (1.07-1.73)
		2004-07	55	155	2.81 (2.39-3.29)	2	59	29.96 (22.81-38.65)	53	96	1.81 (1.46-2.21)
		2008-11	37	141	3.81 (3.21-4.5)	2	81	34.97 (27.77-43.47)	35	60	1.73 (1.32-2.23)
	OESOPHAGUS	2000-03	29	49	1.7 (1.25-2.24)	1	7	7.47 (3-15.39)	28	42	1.5 (1.08-2.03)
		2004-07	28	57	2.04 (1.55-2.65)	1	8	7.79 (3.36-15.35)	27	49	1.82 (1.35-2.41)
		2008-11	19	58	3.04 (2.31-3.93)	1	23	19.52 (12.37-29.28)	18	35	1.95 (1.36-2.72)
	STOMACH	2000-03	171	169	0.99 (0.85-1.15)	5	20	3.81 (2.33-5.88)	166	149	0.9 (0.76-1.06)
		2004-07	159	166	1.04 (0.89-1.22)	6	39	6.78 (4.82-9.26)	153	127	0.83 (0.69-0.99)
		2008-11	98	136	1.39 (1.17-1.65)	6	41	6.77 (4.86-9.19)	92	95	1.04 (0.84-1.27)
	COLON AND RECTUM	2000-03	305	407	1.33 (1.21-1.47)	7	76	10.87 (8.56-13.6)	298	331	1.11 (0.99-1.24)
		2004-07	320	543	1.7 (1.56-1.85)	10	158	15.65 (13.3-18.29)	310	385	1.24 (1.12-1.37)
		2008-11	209	464	2.22 (2.02-2.43)	13	215	16.62 (14.47-19)	196	249	1.27 (1.12-1.44)
	LARYNX	2000-03	26	41	1.55 (1.11-2.1)	1	12	13.98 (7.22-24.42)	26	29	1.13 (0.76-1.63)
		2004-07	27	69	2.56 (1.99-3.23)	1	27	28.04 (18.48-40.79)	26	42	1.61 (1.16-2.18)
		2008-11	19	60	3.19 (2.44-4.11)	1	31	25.9 (17.6-36.76)	18	29	1.65 (1.1-2.37)
	TRACHEA, BRONCHI AND LUNG	2000-03	192	307	3.19 (2.44-4.11)	5	44	9.56 (6.95-12.83)	187	263	1.4 (1.24-1.58)
		2004-07	202	334	1.65 (1.48-1.84)	7	54	7.86 (5.91-10.26)	195	280	1.43 (1.27-1.61)
		2008-11	136	303	2.23 (1.99-2.5)	8	100	12.48 (10.15-15.18)	128	203	1.59 (1.38-1.82)
	PROSTATE	2000-03	434	274	0.63 (0.56-0.71)	11	23	2.08 (1.32-3.12)	423	251	0.59 (0.52-0.67)
		2004-07	434	299	0.69 (0.61-0.77)	16	27	1.72 (1.13-2.5)	418	272	0.65 (0.58-0.73)

FEMALES	KIDNEY	2008-11	279	249	0.89 (0.78-1.01)	17	48	2.81 (2.07-3.72)	262	201	0.77 (0.66-0.88)
		2000-03	32	58	1.8 (1.37-2.32)	1	8	11.13 (4.8-21.93)	32	50	1.59 (1.18-2.09)
		2004-07	36	84	2.31 (1.84-2.85)	1	23	22.69 (14.39-34.05)	35	61	1.72 (1.32-2.21)
		2008-11	26	70	2.7 (2.1-3.41)	2	27	17.89 (11.79-26.03)	24	43	1.76 (1.27-2.37)
	BLADDER	2000-03	135	161	1.19 (1.01-1.39)	4	22	6.18 (3.87-9.36)	132	139	1.06 (0.89-1.25)
		2004-07	131	180	1.37 (1.18-1.59)	5	28	6.15 (4.09-8.89)	127	152	1.2 (1.02-1.4)
		2008-11	80	113	1.4 (1.16-1.69)	5	16	3.19 (1.82-5.18)	75	97	1.29 (1.04-1.57)
	NON-HODGKIN LYMPHOMA	2000-03	44	52	1.17 (0.87-1.54)	1	6	5.74 (2.1-12.48)	43	46	1.06 (0.78-1.42)
		2004-07	48	54	1.13 (0.85-1.48)	17	4	0.23 (0.06-0.59)	30	50	1.65 (1.22-2.17)
		2008-11	32	46	1.43 (1.04-1.9)	2	11	5.92 (2.95-10.59)	30	35	1.15 (0.8-1.6)
	ALL	2000-03	814	1257	1.54 (1.46-1.63)	16	226	13.99 (12.22-15.94)	798	1031	1.29 (1.21-1.37)
		2004-07	754	1366	1.81 (1.72-1.91)	21	349	16.44 (14.76-18.26)	732	1017	1.39 (1.3-1.48)
		2008-11	538	1254	2.33 (2.2-2.46)	30	486	16.45 (15.02-17.98)	509	768	1.51 (1.4-1.62)
		2000-03	79	100	1.27 (1.03-1.55)	2	17	8.94 (5.21-14.32)	77	83	1.08 (0.86-1.34)
	STOMACH	2004-07	66	73	1.1 (0.87-1.39)	2	18	8.32 (4.93-13.15)	64	55	0.86 (0.65-1.12)
		2008-11	44	76	1.71 (1.35-2.14)	3	30	11.59 (7.82-16.55)	42	46	1.1 (0.81-1.47)
		2000-03	140	256	1.83 (1.61-2.07)	3	42	15.51 (11.18-20.97)	137	214	1.56 (1.36-1.78)
	COLON AND RECTUM	2004-07	129	321	2.49 (2.23-2.78)	4	51	13.06 (9.72-17.17)	125	270	2.16 (1.91-2.44)
		2008-11	88	319	3.63 (3.24-4.05)	5	159	30.95 (26.32-36.15)	83	160	1.93 (1.65-2.26)
		2000-03	36	86	2.41 (1.93-2.98)	1	12	22.12 (11.43-38.64)	35	74	2.11 (1.66-2.65)
	TRACHEA, BRONCHI AND LUNG	2004-07	36	84	2.37 (1.89-2.93)	1	18	19.35 (11.47-30.59)	35	66	1.91 (1.48-2.43)
		2008-11	26	66	2.54 (1.96-3.23)	1	17	12.25 (7.13-19.61)	25	49	1.99 (1.47-2.63)
		2000-03	207	231	1.11 (0.97-1.27)	4	53	13.13 (9.84-17.18)	203	178	0.88 (0.75-1.01)
	BREAST	2004-07	195	261	1.34 (1.18-1.51)	5	82	15.3 (12.17-18.99)	190	179	0.94 (0.81-1.09)
		2008-11	142	237	1.66 (1.46-1.89)	7	105	14.23 (11.64-17.22)	135	132	0.98 (0.82-1.16)
		2000-03	25	48	1.89 (1.39-2.5)	1	13	18.03 (9.6-30.84)	25	35	1.42 (0.99-1.97)
	CERVIX UTERI	2004-07	20	37	1.81 (1.27-2.49)	1	9	13.08 (5.98-24.83)	20	28	1.41 (0.94-2.04)
		2008-11	13	41	3.18 (2.29-4.32)	1	20	25.91 (15.83-40.02)	12	21	1.73 (1.07-2.65)
	CORPUS UTERI	2000-03	37	78	2.11 (1.66-2.63)	1	14	20.33 (11.12-34.12)	36	64	1.76 (1.36-2.25)
		2004-07	35	73	2.09 (1.64-2.63)	1	25	26.15 (16.92-38.61)	34	48	1.41 (1.04-1.88)

	2008-11	24	57	2.39 (1.81-3.1)	1	30	21.13 (14.26-30.17)	22	27	1.2 (0.79-1.75)
	2000-03	16	35	2.24 (1.56-3.12)	0	11	33.65 (16.8-60.22)	15	24	1.57 (1.01-2.34)
OVARY	2004-07	14	33	2.37 (1.63-3.32)	0	10	23.63 (11.33-43.45)	14	23	1.7 (1.08-2.55)
	2008-11	10	38	4 (2.83-5.49)	1	19	36.2 (21.8-56.53)	9	19	2.12 (1.27-3.3)
	2000-03	23	29	1.25 (0.84-1.79)	1	4	7.37 (2.01-18.87)	23	25	1.1 (0.71-1.63)
BLADDER	2004-07	20	49	2.41 (1.79-3.19)	1	6	9.94 (3.65-21.64)	20	43	2.18 (1.58-2.94)
	2008-11	14	26	1.82 (1.19-2.67)	1	5	6.06 (1.97-14.15)	13	21	1.56 (0.97-2.39)
	2000-03	44	51	1.15 (0.86-1.51)	1	6	9.74 (3.57-21.2)	44	45	1.03 (0.75-1.38)
THYROID	2004-07	46	69	1.48 (1.15-1.88)	1	7	6.36 (2.56-13.1)	45	62	1.37 (1.05-1.75)
	2008-11	35	64	1.84 (1.42-2.35)	2	7	3.89 (1.56-8.01)	33	57	1.73 (1.31-2.24)
	2000-03	28	32	1.13 (0.77-1.59)	1	6	11.05 (4.06-24.06)	28	26	0.93 (0.61-1.37)
NON-HODGKIN LYMPHOMA	2004-07	26	33	1.25 (0.86-1.76)	1	4	5.33 (1.45-13.65)	26	29	1.13 (0.76-1.63)
	2008-11	19	41	2.15 (1.54-2.92)	1	13	12.72 (6.77-21.76)	18	28	1.55 (1.03-2.24)

SIR – Standardized Incidence Ratios, SPC – Second Primary Cancer, 95% CI – 95% Confidence Interval.

^a Lip, oral cavity and pharynx (C00–C14), Oesophagus (C15), Stomach (C16), Colon and rectum (C18–C20), Larynx (C32), Trachea, bronchi and lung (C33–C34), Female breast (C50), Cervix uteri (C53), Corpus uteri (C54), Ovary (C56), Prostate (C61), Kidney (C64), Bladder (C67), Thyroid (C73), Non-Hodgkin Lymphoma (C82–86, C96) defined according to the International Statistical Classification of Diseases and Related Health Problems, 10th Revision.

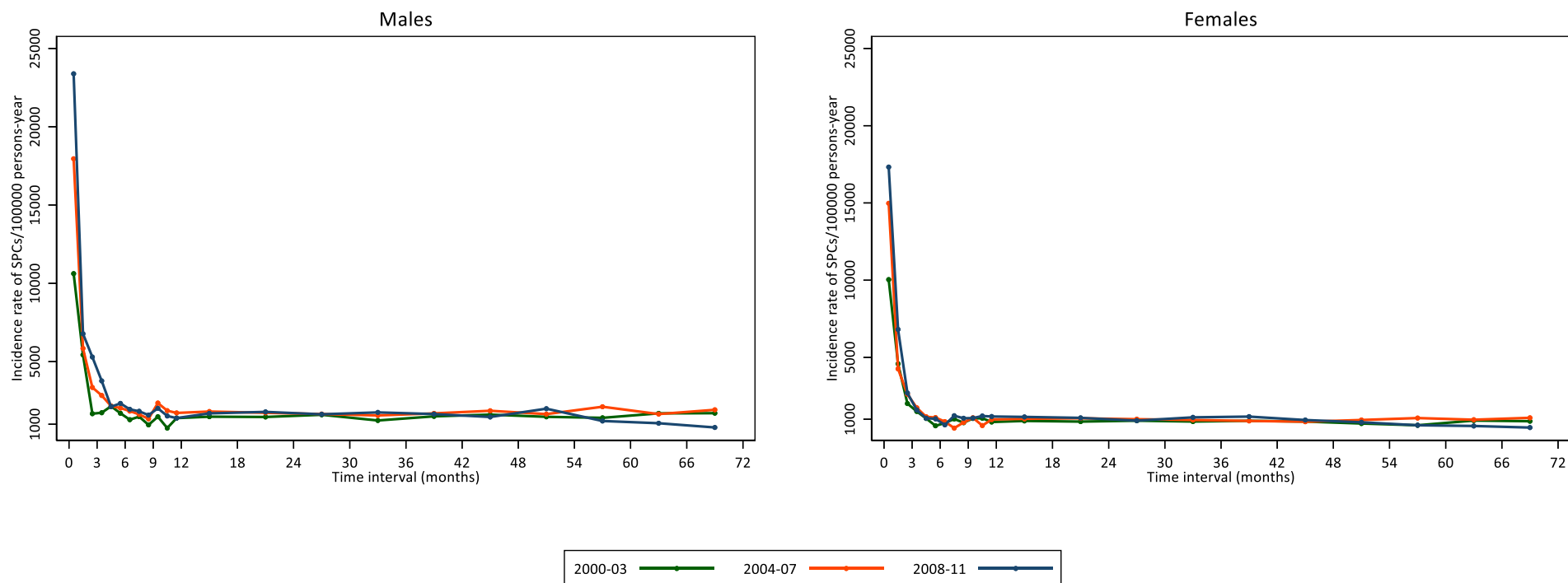


Figure 1. Trends in incidence rates of all second primary cancers since the diagnosis of a first primary cancer by calendar year of first primary cancer diagnosis (2000–03, 2004–07, 2008–11) among males and females.

SPCs – Second Primary Cancers.

Incidence rates were estimated for and represented in the respective midpoint of the following intervals: 0 to <1 month, ≥ 1 to <2 months, ≥ 2 to <3 months, ≥ 3 to <4 months, ≥ 4 to <5 months, ≥ 5 to <6 months, ≥ 6 to <7 months, ≥ 7 to <8 months, ≥ 8 to <9 months, ≥ 9 to <10 months, ≥ 10 to <11 months, ≥ 11 to <12 months, and then for each six months of follow-up until 72 months.

**Second primary cancers among females with a first primary
breast cancer: a population-based study in Northern Portugal**



Second primary cancers among females with a first primary breast cancer: a population-based study in Northern Portugal

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Abstract

Purpose To estimate the incidence rate of second primary cancers (SPCs) and the cumulative incidence of metachronous [diagnosed > 2 months after a first primary cancer (FPC)] SPCs in patients with a breast FPC, and to compare the incidence of SPC [overall, synchronous (≤ 2 months of the FPC) and metachronous] with that expected in the general female population. **Methods** A cohort of patients with a breast FPC from the North Region Cancer Registry of Portugal, diagnosed in 2000–2010 ($n = 15,981$), was followed to 31 December 2015 for synchronous and metachronous SPCs. Cumulative incidence of metachronous SPCs considering death as a competing event, and incidence rates and standardized incidence ratios of SPCs were estimated.

Results The diagnosis of an SPC occurred in 1229 (7.7%) of patients with a breast FPC. SPCs occurred mainly in the breast, followed by digestive organs, lung, thyroid, and female genital organs. Globally, patients with a breast FPC had a higher incidence for all types of cancer compared to the general female population, and in particular for cancers of the breast, stomach, colon, lung, lymphoma, uterus, and ovary. The 10-year cumulative incidence of metachronous SPCs following a breast FPC was 6.6% and the corresponding 10-year cumulative mortality was 26.2%.

Conclusion In Portugal, patients with a breast FPC have a higher incidence of cancer compared to the general female population, highlighting important aspects of care, surveillance, and counselling among this growing number of patients.

Keywords Breast neoplasms · Epidemiology · Population register · Second primary neoplasm

Introduction

Worldwide, breast cancer represents the most common tumor diagnosed and the fifth leading cause of death, accounting for an estimated 2.3 million new cases and 685 thousand

deaths in 2020. Further, breast cancer is the world's most prevalent cancer with nearly eight million women alive who were diagnosed in the past five years [1].

The diagnosis of a second primary cancer (SPC) after breast cancer has increased over the last 20 years [2–6].

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The early diagnosis of breast cancer because of screening programs, overall improvements in accessibility to health care, effective imaging, and treatments, including less invasive surgery, have improved survival [2, 7, 8]. Survivors of breast cancer are at risk of subsequent primary cancers due to common genetic, environmental, and hormonal etiological factors, as well as side effects of therapy for a previous cancer [2, 7].

The burden of an SPC among patients with breast cancer has been previously described. In general, the overall excess incidence for developing an SPC in female patients with breast cancer, compared to the general population, has been reported to range from 18% to 30%, with higher incidences associated with early onset breast cancer diagnosis [7–12]. The most common SPC sites in the literature include female genital organs [7, 10–15], digestive organs [7, 10–13], lung [10, 12, 13], melanoma [7, 10, 11, 15], leukemia [10, 13, 14], thyroid [12, 15] and sarcoma [10, 14, 15].

The development of an SPC among a high incident tumor, such as breast cancer [16], may impair survivor expectations, surveillance protocols and increasingly burden the healthcare system [5, 6, 11, 15]. In Portugal, the incidence and risk of SPCs following a breast FPC has not yet been evaluated at the population level. This study aimed to calculate the incidence rates of SPCs and the corresponding standardized incidence ratios (SIRs), and to estimate the probability of being diagnosed with an SPC up to 10-years after a breast FPC, diagnosed between 2000 and 2010, in the North of Portugal.

Methods

Study setting

Cancer data were provided by the North Region Cancer Registry (RORENO), a population-based cancer registry established in 1988. The registry covers the Northern region of Portugal, corresponding to approximately 3.3 million inhabitants, which is nearly one-third of the Portuguese population [17]. Registration follows the International Agency for Research on Cancer (IARC) rules, which include four quality dimensions: comparability, validity, timeliness, and completeness. Registries maintain quality through regular screening with pre-defined algorithms for validity and consistency [18]. From 1998 to 2002, RORENO fulfilled IARC indices of data quality, which indicates a high degree of completeness of ascertainment [18].

Tumour classification and definition of multiple primary cancers

Tumour topography and morphology were classified according to the International Classification of Diseases for Oncology, Third Edition [19], and then recoded to the International Statistical Classification of Diseases and Related Health Problems 10th Revision [20].

SPC is a new primary cancer in a person with a history of malignancy. Multiple primary cancers were defined according to the guidelines proposed by the International Association of Cancer Registries (IACR) and IARC [21]. Briefly, these guidelines consider primary cancers those that originally developed in an organ or tissue, not being an extension, recurrence, or metastasis. Different morphologies (even with the same topography) or dissimilar topographies should be regarded as multiple primary cancers, regardless of the time between diagnoses, unless they correspond to systemic cancers, which are considered the same cancer [21].

Study design

All primary invasive tumours of the breast (C50) diagnosed in adult female residents in the North of Portugal between 1 January 2000 and 31 December 2010 were identified ($n=17,210$).

Patients who had a cancer diagnosis, except skin non melanoma, previous to a breast cancer ($n=1064$) and those who could not be linked to the National Health Service for assessment of vital status ($n=165$) were excluded. The latter were older at diagnosis of the breast FPC than included patients [median (percentile 25 – percentile 75 (P25–P75)): included – 57 (47–68) vs. excluded – 59 (48–76); $p=0.058$].

The remaining patients ($n=15,981$) were followed to 31 December 2015, allowing for five to 16 years of potential follow-up, until the diagnosis of an SPC or death, whichever occurred first. The occurrence of any subsequent cancer was ascertained by means of linkage with the list of cases registered by RORENO. Patients known to have died but with an unknown date of death ($n=7$), were imputed a follow-up time equal to the median follow-up of the corresponding five-year age group (from 15–19 to 70–74, and ≥ 75) and year of diagnosis.

If more than two primary cancers were observed in the same patient, only the SPC was considered; third and subsequent primaries were disregarded. Due to the thorough evaluation of cancer patients during the initial medical work-up, SPCs were classified as synchronous when diagnosed within two months of the breast FPC or metachronous otherwise, as in previous studies [16, 22, 23].

Statistical analysis

Patients' characteristics were presented as counts and proportions for categorical variables, and median (P25-P75) for continuous variables. To compare quantitative and categorical variables across groups, the Mann-Whitney test and Chi-square test were used, respectively. Statistical significance was considered when $p < 0.05$. All reported p -values were two-sided. Analyses were carried out separately for synchronous and metachronous SPCs.

Person-years at risk (PYAR) were calculated as the time from breast FPC diagnosis to the SPC diagnosis, death, or end of follow-up (31 December 2015), whichever occurred first. The incidence rate of SPCs was computed for different follow-up periods ("0 to < 1 month" – from FPC diagnosis to less than one month; "≥ 1 to < 2 months" – from one to less than two months; "≥ 2 to < 3 months" – from two to less than three months and so on during the first year of follow-up; "≥ 12 to < 18 months" – from 12 to less than 18 months; "≥ 18 months to 24 months" – from 18 months to less than 24 months and so on to the sixth year of follow-up; and then for each year of follow-up), by dividing the number of incident SPCs by the PYAR within each time interval.

The incidence of SPCs was compared with age- and calendar year-specific rates in the general female population from Northern Portugal, by calculating SIRs. These were calculated by dividing the observed number of SPCs by the expected number of cases, in the same time period, if the cancer incidence rates in the general female population had been observed among survivors of breast FPC. The latter were estimated by multiplying the cancer incidence in the general female population by the PYAR in the corresponding stratum defined according to five-year age group (from 15–19 to 70–74, and ≥ 75 years) and calendar year (2000–2015). The incidence of cancer [overall and for specific cancers: stomach, colon, rectum, liver, lung, breast, cervix uteri, corpus uteri, ovary, kidney, bladder, thyroid, non-Hodgkin lymphoma (NHL)] among the general female population was acquired from RORENO [17]. The 95% confidence intervals (CIs) of the SIRs were estimated assuming that the number of cancers followed a Poisson probability distribution. SIRs and the corresponding 95%CIs were estimated for two different periods: "0–2 months" – from FPC diagnosis to two months of follow-up; "> 2 months" – from two months to the end of follow-up.

Cumulative incidence and corresponding 95%CIs, stratified by age were calculated, for all and metachronous SPCs, considering death as a competing event according to the method of Kalbfleisch and Prentice [24].

Additionally, several sensitivity analyses were performed defining SPCs as diagnosed six months and one year after the breast FPC.

Statistical analyses were conducted using STATA®15.1.

Results

Among 15,981 patients with a breast FPC diagnosed between 2000 and 2010, 1229 (7.7%) developed an SPC during follow-up, from which 215 (17.5%) were diagnosed within the first two months of the breast FPC. The median age at diagnosis of a breast FPC was 57 years (Table 1). Patients who developed an SPC were generally older at breast FPC diagnosis compared to those without an SPC. Bilateral breast cancer was identified in 57 patients, which were considered a synchronous SPC. The median time follow-up was nearly 10 years for all patients, and the median time between breast FPC and metachronous SPC diagnosis was close to five years.

Incidence rate of second primary cancers and standardized incidence ratios

A very high incidence rate of SPCs was identified in the first two months (Fig. 1). The incidence rate of SPCs was over 14-fold higher in the first few months of follow-up than in the remaining period. Incidence rates remained relatively stable from 12 months on with 1000 SPCs/100,000 persons-year.

The majority of SPCs occurred in the breast with a large number occurring within two months of the FPC diagnosis. Digestive organs were the second most common SPC, namely stomach, colon, and rectum, followed by lung, thyroid, and female genital organs (Fig. 2).

SIRs for all, synchronous and metachronous SPCs are summarized in Fig. 3. Overall, patients with a breast FPC had a higher incidence of all types of cancer compared to the general female population ($SIR = 1.36$; 95%CI: 1.28, 1.43). The most relevant sites were stomach ($SIR = 1.29$; 95%CI: 1.05, 1.57), colon ($SIR = 1.43$; 95%CI: 1.21, 1.68), liver ($SIR = 2.62$; 95%CI: 1.64, 3.97), lung ($SIR = 2.04$; 95%CI: 1.63, 2.52), breast ($SIR = 1.35$; 95%CI: 1.21, 1.50), corpus uteri ($SIR = 1.89$; 95%CI: 1.50, 2.37), ovary ($SIR = 1.56$; 95%CI: 1.02, 2.29), bladder ($SIR = 1.57$; 95%CI: 1.10, 2.19), thyroid ($SIR = 1.31$; 95%CI: 1.04, 1.63) and NHL ($SIR = 1.43$; 95%CI: 1.04, 1.91). Increased SIRs for synchronous SPCs were observed for the stomach ($SIR = 4.16$; 95%CI: 1.53, 9.05), colon ($SIR = 4.02$; 95%CI: 1.62, 8.29), breast ($SIR = 39.92$; 95%CI: 34.25, 46.25) and NHL ($SIR = 5.74$; 95%CI: 1.18, 16.78). SIR estimates for metachronous SPCs did not markedly differ from estimates for all SPCs of the same SPC type.

Table 1 Features of female breast cancer patients with synchronous and metachronous second primary cancers, and without a second primary cancer

	Total		Patients without an SPC		Patients with an SPC				
	N=15,981 (100.0%)		N=14,752 (92.3%)	<i>p</i> -value All SPC vs. no SPC	Synchronous (n=215)	<i>p</i> -value Synchronous SPC vs. no SPC		Metachronous (n=1014)	<i>p</i> -value Metachronous SPC vs. no SPC ^a
Age at diagnosis of BCa, years [median (P25-P75)]	57 (47–68)		56 (47–68)	<0.001	61 (49–72)	0.006	60 (50–70)	<0.001	0.880
<45	3032 (19.0%)		2879 (19.5%)		30 (13.9%)		123 (12.1)		
45–54	4162 (26.0%)		3874 (26.3%)		57 (26.5%)		231 (22.8%)		
55–64	3565 (22.3%)		3267 (22.2%)		42 (19.5%)		256 (25.2%)		
65–74	2945 (18.4%)		2639 (17.9%)		48 (22.3%)		258 (25.4%)		
≥75	2274 (14.2%)		2090 (14.2%)	<0.001	38 (17.7%)	0.122	146 (14.4%)	<0.001	0.208
BCa laterality									
Right	5839 (36.5%)		5392 (36.5%)		76 (35.3%)		371 (36.6%)		
Left	6490 (40.6%)		5980 (40.5%)		67 (31.2%)		443 (43.7%)		
Bilateral	57 (0.4%)		--		57 (26.5%)		--		
Unknown/missing	3595 (22.5%)		3380 (22.9)	<0.001	15 (7.0%)	<0.001	200 (19.7%)	0.052	<0.001
Follow-up, years [median (P25-P75)] ^b	9.7 (7.2–12.5)		9.5 (7.1–12.4)	<0.001	0.1 (0.0–0.1)	<0.001	4.9 (2.3–7.8)	<0.001	<0.001
Dead [N (%)]^c	4663 (29.2%)		4111 (27.9%)	<0.001	93 (43.3%)	<0.001	459 (45.3%)	<0.001	0.590

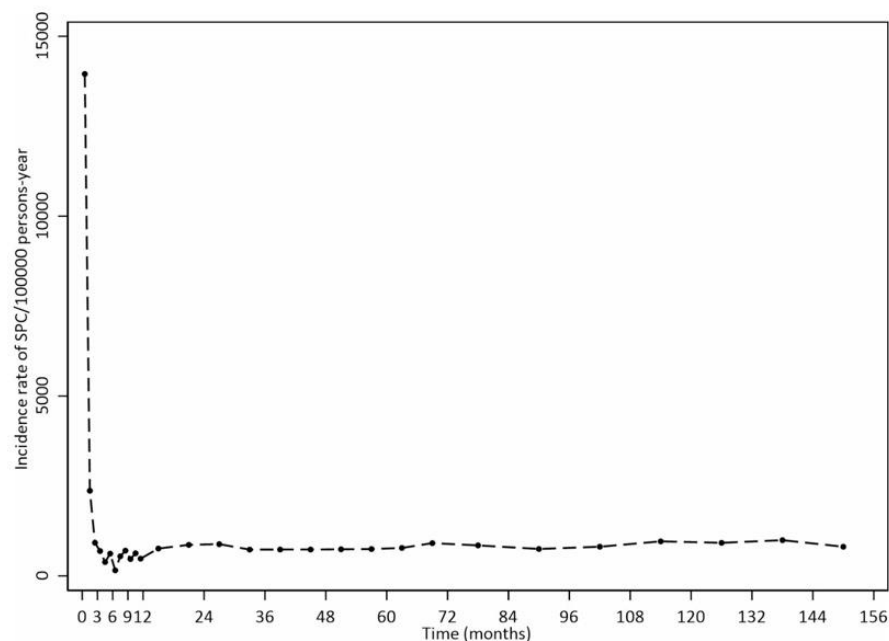
BCa, breast cancer; P25, percentile 25; P75 percentile 75; SPC, second primary cancer

BCa, breast cancer, P25, percentile 25; P75 percentile 75; SPC, second primary cancer

May not add to 15,981 due to missing data

^a Patients without an SPC are those who survived more than two months after diagnosis of the FPC^b Follow-up to 31 December 2015 until SPC, death or end of follow-up. Median follow-up time was estimated using the reverse Kaplan-Meier^c Follow-up to 31 December 2015

Fig. 1 Incidence rates of second primary cancers since the diagnosis of the first primary breast cancer. FPC, first primary cancer; SPC, second primary cancer. Incidence rates were estimated for and represented in the respective midpoint of the following intervals: each month in the first year of follow-up, every six months from the second to the sixth year of follow-up, and then for each year of follow-up



Cumulative incidence of metachronous second primary cancers and death

The five- and 10-year cumulative incidence for metachronous SPCs following a breast FPC, was 3.3% (95%CI: 3.0, 3.6) and 6.6% (95%CI: 6.2–7.0), respectively (Fig. 4). The corresponding five- and 10-year cumulative mortality was 16.0% (95%CI: 15.4, 16.6) and 26.2% (95%CI: 25.5, 27.0). Generally, the cumulative incidence of SPC was higher among older women (Supplementary Table 1).

Sensitivity analysis

Analyses defining synchronous SPCs as occurring within two, six and 12 months of a breast FPC resulted in SIRs of 13.57 (95%CI: 11.82, 15.51), 5.30 (95%CI: 4.66, 6.00) and 3.06 (95%CI: 2.72, 3.44), respectively (Supplementary Table 2). Stomach, colon, liver, lung, breast, uterus followed by bladder and thyroid were the most frequent SPCs diagnosed among patients with breast FPC regardless of the time used to define the cut-off. Considering the complementary definition for metachronous SPCs, SIRs at two and six months were 1.14 (95%CI: 1.07, 1.21) and for 12 months 1.16 (95%CI: 1.09, 1.23; Supplementary Table 3). The 10-year cumulative incidence was 6.6%, 6.7% and 7.0% when defining metachronous SPC as two, six and 12 months, respectively.

Discussion

In Northern Portugal, patients with a breast FPC had a higher incidence of cancer compared with the general female population. The majority of SPCs occurred in the breast, followed by digestive organs, lung, thyroid, and female genital organs. The cumulative incidence of metachronous SPCs was 6.6% at 10 years and the corresponding estimate for mortality was 26.2%.

Several population-based cancer registry studies have been published on the occurrence of SPC among patients with a breast FPC [5, 7, 12–14]. Previously, our working group assessed the risk and survival of third primary cancers in this cohort [25], nevertheless this is the first Portuguese population-based study with a focus on SPCs among patients with a breast FPC.

In the current study, we found SPCs were diagnosed most often in the breast, digestive organs, lung, thyroid, and female genital organs, which is in line with results from previous studies. A Spanish cohort study reported skin, ovary, uterus, colorectal, stomach and thyroid cancers to be the most frequent SPCs [7]. A Danish population-based registry study identified the uterus, ovary, soft tissue, leukemia and colon as the most common SPC following a breast cancer diagnosis [14]. From Israel, Silverman et al. found colorectal, uterine, lung, ovarian, thyroid and leukemia to be the most common sites for an SPC after a breast cancer diagnosis [26]. In the US, the SPCs most commonly diagnosed were bone, breast, leukemia, lung, and ovary [13]. More recently, a systematic review and meta-analysis by Allen

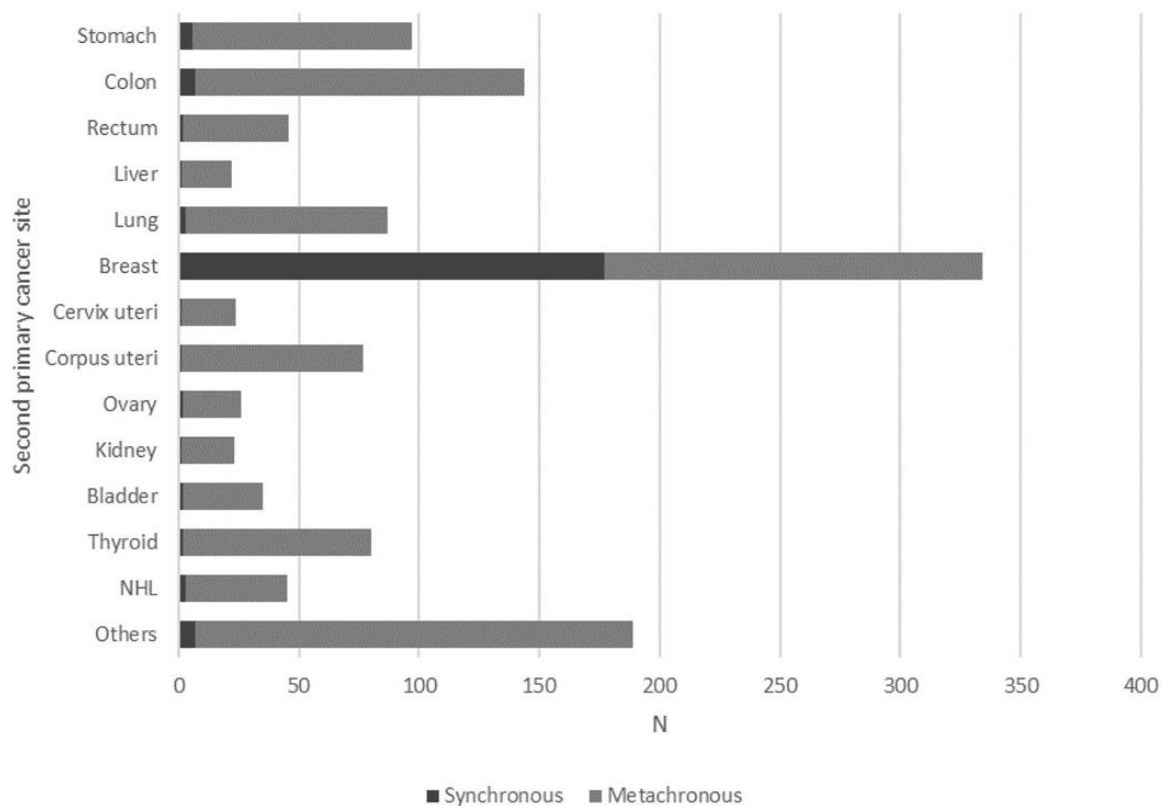


Fig. 2 Distribution of synchronous and metachronous second primary cancers^a among females with a first primary breast cancer. NHL, non-Hodgkin lymphoma. ^a Stomach (C16), Colon (C18), Rectum (C19–C20), Liver and intrahepatic bile ducts (C22), Lung (including trachea and bronchus; C33–C34), Breast (C50), Cervix uteri (C53), Corpus uteri (C54), Ovary (C56), Kidney (C64), Bladder (C67), Thyroid (C73), Non-Hodgkin lymphoma (C82–C86, C96). Others include: Lip, oral cavity and pharynx (C1–C14), Oesophagus (C15), Small intestine (C17), Anus (C21), Gallbladder, and other and unspecified parts of biliary tract (C23–C24), Pancreas (C25), Nasal cavity and middle ear

(C30), Larynx (C32), Other and ill-defined sites in the respiratory system and intrathoracic organs (C39), Bone and articular cartilage (C40–C41), Kaposi sarcoma (C46), Other connective and soft tissue (C49), Vulva (C51), Vagina (C52), Uterus, part unspecified (C55), Ureter (C66), Brain and central nervous system (C70–C72), Without specification of site (C80), Lymphoid leukaemia (C91), Myeloid leukaemia (C92–C94), Leukaemia of unspecified cell type (C95), Myelodysplastic syndromes (D46), Other neoplasms of uncertain or unknown behaviour of lymphoid, haematopoietic and related tissue (D47) [19]

et al., found female patients with breast cancer were more commonly diagnosed with an SPC of the thyroid, endometrium, ovary, kidney, esophagus, skin, lung, leukemia, and stomach [5].

Patterns between breast FPC and SPC sites are complex and multifactorial [14]. SPCs may occur because of common lifestyle risk factors, reproductive and hormonal exposures, and genetic predisposition [2, 4, 9, 14]. Obesity, tobacco smoking and high blood pressure have also been described as risk factors for SPC [3]. The combination of early menarche, low parity, and late menopause, and non-users of contraceptive pill have also been shown to be associated with SPC among patients with a previous breast cancer diagnosis [3, 9]. Genetic mutations, such as BRCA, PTEN and TP53, also increase the incidence of SPCs, namely contralateral

breast cancer, female genital organs, pancreas, and thyroid [2, 5, 14]. Moreover, the occurrence of SPCs may reflect the late effects of cancer treatments, namely radiotherapy and tamoxifen [4, 7, 9]. Radiotherapy is protocolled as an adjuvant therapy for conservative treatment; and more recently, there is an increased awareness regarding radiation and the occurrence of SPCs [27], particularly in adjacent organs of exposure [4, 14, 27]. Tamoxifen therapy for breast cancer, a standard of care for those expressing hormone-receptors, also contributes to SPCs, specifically in the uterus [7, 11], since it enables estrogen metabolism and malignant transformation [2].

Generally, studies report increased SIRs of cancer among patients with breast cancer compared with general female population [5, 7, 12–14], which is in line with our findings.

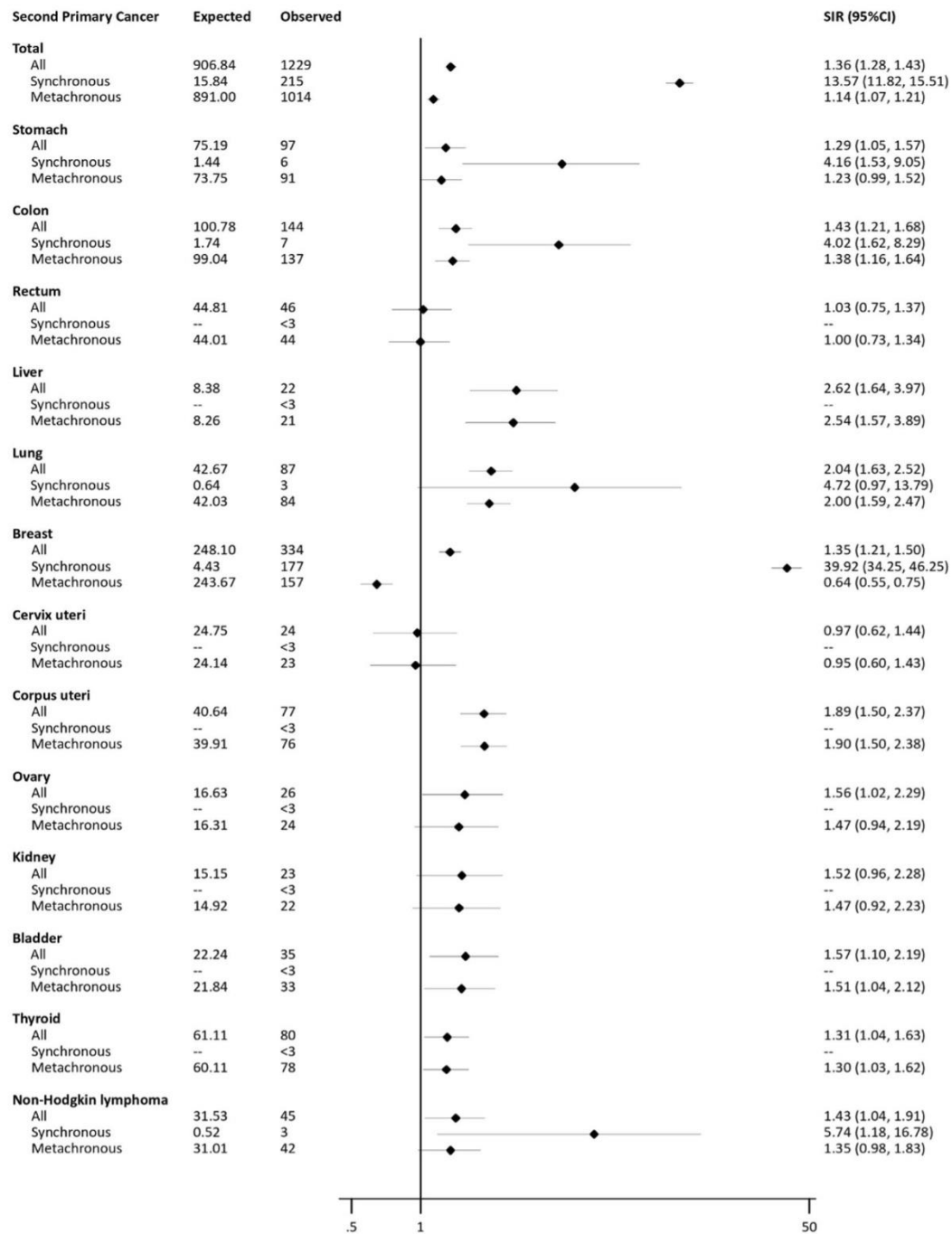


Fig. 3 Standardized incidence ratios and 95% confidence interval of selected second primary cancers^a in patients with first primary breast cancer. 95%CI, 95% confidence interval; SIR, standardized incidence ratios; --, expected number of SPCs and SIRs (95%CI) were not estimated as less than three SPCs were observed. ^a Stomach (C16), Colon

(C18), Rectum (C19-C20), Liver and intrahepatic bile ducts (C22), Lung (including trachea and bronchus; C33-C34), Breast (C50), Cervix uteri (C53), Corpus uteri (C54), Ovary (C56), Kidney (C64), Bladder (C67), Thyroid (C73), Non-Hodgkin lymphoma (C82-C86, C96) [19]

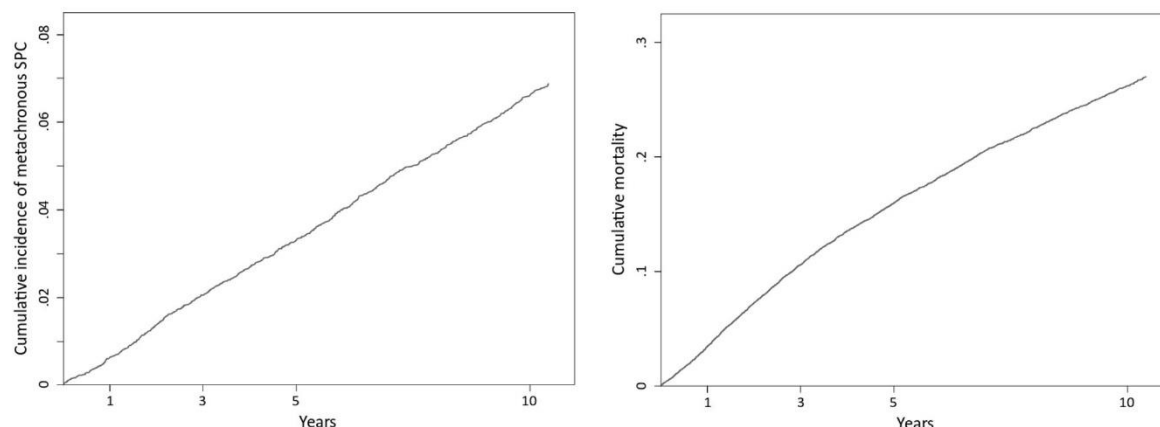


Fig. 4 Cumulative incidence of metachronous second primary cancers and death, considering the competing event of death, among females with a first primary breast cancer. SPC, second primary cancer. * Note that a different scale is used for the two outcomes

A Danish Cancer Registry study by Andersson et al. evaluated non-breast metachronous SPCs among nearly 32 thousand patients with breast cancer diagnosed between 1977 and 2001, and reported a SIR of 1.04 [14]. In Spain, a SIR of 1.39 for non-breast metachronous SPCs was estimated among a cohort of close to 6000 patients with breast cancer followed for 22 years [7]. From Israel, a study conducted among a 46 thousand cohort of women diagnosed with breast cancer between 1990 and 2006 found an overall SIR for non-breast SPCs of 1.26; the corresponding estimate for metachronous SPCs was 1.21 [26]. A study by Hung et al. in Taiwan involving over 100 thousand female patients with breast cancer diagnosed between 1997 and 2011, estimated a SIR of 1.51 for non-breast SPCs [15]. Finally, a US cohort of 335 thousand patients registered in the National Cancer Institute's Surveillance Epidemiology and End Results (SEER) database and diagnosed with breast cancer from 1973 to 2000, identified an overall SIR of 1.33 for all SPCs [13].

Time elapsed since a breast cancer diagnosis, calendar year of breast cancer diagnosis, related to different trends in incidence and mortality because of improved diagnosis and treatment, and geographic region could justify the variations observed. Moreover, different coding rules are used across the studies to define SPCs, which impact these estimates [3, 6]. Some authors did not assess contralateral breast SPC, arguing a lack of information on histology for breast cancer, and preferred to avoid misclassification of a recurrence or a new primary cancer as an SPC [10, 12]. We used IARC rules to define SPCs and as such, included bilateral and contralateral breast cancers as SPCs [18]. Nevertheless, our SIR estimates remained statistically significant even when excluding the 57 patients with bilateral breast cancer [SIR

for all SPC=1.29 (95%CI: 1.22, 1.37); SIR for synchronous SPCs=9.72 (95%CI: 8.25, 11.38)].

We observed higher cumulative incidence estimates among older patients diagnosed with a breast FPC. Few studies in the literature provide cumulative incidence estimates for SPCs among patients with breast cancer. Li et al. described a cumulative incidence of SPCs of 7.4% at 10 years and 20.1% at 20 years [4], and Lee et al. a cumulative incidence of SPCs (excluding those diagnosed within one month of the FPC) of nearly 1% and 2% at five years and 2% and 4% at 10 years, for patients under fifty years and over, respectively [12].

Strengths and limitations

Our data was obtained from a population-based registry, RORENO, which is highly representative of patients with breast cancer from Northern Portugal, as such, extrapolating these results to all patients with breast cancer in Portugal should be done cautiously since the incidence and mortality of breast cancer within the country differs [28, 29]. Nevertheless, our study has a large catchment area, a long-term and complete follow-up with only 1% losses identified, and there is universal, free access to healthcare. However, some limitations should be highlighted. Information on clinical data was missing, namely stage at FPC and SPC diagnosis, hormonal receptor status of the tumor, treatment regime, as well as information on lifestyle (diet, smoking, alcohol) and menopausal status, family history or genetic susceptibility. We were unable to quantify their contribution, which have been shown by some studies to be associated with higher-than-expected SPCs [2, 4, 9, 14].

Conclusion

The present study shows that female patients with breast cancer have a higher incidence of cancer compared with the general female Northern Portuguese population. Besides the impact on public health, our work highlights the need for the surveillance of survivors of breast cancer, a number that is continuously growing. A regular follow-up through comprehensive care, active treatment of the SPC, considering the previous toxicities and an effective approach to the expectations of the survivors of breast cancer are challenges to improve the quality of life of patients.

Abbreviations

95%CI	95% confidence interval
BCa	Breast cancer
FPC	First primary cancer
IACR	International Association of Cancer Registries
IARC	International Agency for Research on Cancer
NHL	Non-Hodgkin lymphoma
P25-P75	Percentile 25 – percentile 75
PYAR	Person-years at risk
RORENO	North Region Cancer Registry of Portugal
SIR	Standardized incidence ratios
SPC	Second primary cancer
US	United States

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Author contributions All authors contributed to the study conception and design. Data preparation and collection were performed by Elisabete Gonçalves, Jéssica Rocha Rodrigues, Rita Calisto, Maria José Bento, and Samantha Morais. Analyses were performed by Elisabete Gonçalves and Samantha Morais. The first draft of the manuscript was written by Elisabete Gonçalves, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability The data that support the findings of this study are available from RORENO, but restrictions apply to the availability of

these data, which were used under license for the current study and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of RORENO.

Declarations

Ethics approval The study was approved by the Ethics Committee of the Portuguese Institute of Oncology of Porto (Ref. CES IPO: 332/020) and the analyses were performed according to RORENO guidelines ensuring the anonymity of information used.

Competing interests The authors have no relevant financial or non-financial interests to disclose.

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Supplementary Table 1. Cumulative incidence of second primary cancers considering the competing event of death, and cumulative mortality.

		Cumulative incidence of SPC [% (95%CI)]				Cumulative mortality [% (95%CI)]			
Years		1	3	5	10	1	3	5	10
Total		1.0 (0.9-1.2)	2.5 (2.3-2.8)	3.7 (3.5-4.0)	7.0 (6.6-7.5)	3.6 (3.3-3.8)	10.7 (10.2-11.2)	16.2 (15.6-16.7)	26.4 (25.7-27.2)
All SPC	Age at BCa diagnosis, years								
	<45	0.7 (0.4-1.0)	1.6 (1.1-2.0)	2.2 (1.7-2.8)	4.8 (3.9-5.6)	1.4 (0.9-1.8)	6.7 (5.8-7.6)	11.1 (10.0-12.2)	18.1 (16.6-19.5)
	45-54	0.9 (0.6-1.2)	2.1 (1.6-2.5)	3.2 (2.7-3.8)	6.0 (5.2-6.8)	1.2 (0.8-1.5)	5.9 (5.2-6.6)	9.4 (8.5-10.2)	15.5 (14.3-16.7)
	55-64	0.7 (0.4-1.0)	2.5 (2.0-3.0)	3.8 (3.1-4.4)	7.8 (6.8-8.8)	2.7 (2.1-3.2)	7.4 (6.6-8.3)	12.3 (11.2-13.4)	20.4 (18.9-21.8)
	65-74	1.5 (1.1-1.9)	3.5 (2.8-4.1)	5.1 (4.3-5.9)	9.6 (8.4-10.7)	3.6 (2.9-4.3)	11.1 (9.9-12.2)	16.2 (14.9-17.6)	28.5 (26.7-30.3)
	≥75	1.6 (1.0-2.1)	3.4 (2.7-4.2)	4.9 (4.0-5.8)	7.6 (6.4-8.7)	12.2 (10.9-13.6)	29.7 (27.8-31.5)	41.5 (39.5-43.5)	65.1 (62.8-67.4)
Metachronous SPC	Total	0.6 (0.5-0.7)	2.0 (1.8-2.3)	3.3 (3.0-3.6)	6.6 (6.2-7.0)	3.5 (3.2-3.8)	10.6 (10.1-11.1)	16.0 (15.4-16.6)	26.2 (25.5-27.0)
	Age at BCa diagnosis, years								
	<45	0.4 (0.2-0.6)	1.2 (0.8-1.5)	1.9 (1.4-2.3)	4.4 (3.5-5.2)	1.8 (1.3-2.2)	6.9 (6.0-7.8)	11.3 (10.2-12.5)	18.1 (16.6-19.6)
	45-54	0.4 (0.2-0.5)	1.5 (1.2-1.9)	2.7 (2.2-3.2)	5.5 (4.7-6.3)	1.4 (1.0-1.8)	6.1 (5.4-6.9)	9.5 (8.6-10.4)	15.5 (14.3-16.7)
	55-64	0.5 (0.2-0.7)	2.2 (1.7-2.7)	3.4 (2.8-4.0)	7.6 (6.6-8.6)	2.5 (2.0-3.1)	7.4 (6.5-8.3)	12.3 (11.2-13.4)	20.3 (18.9-21.8)
	65-74	0.9 (0.6-1.3)	2.8 (2.2-3.4)	4.7 (3.9-5.4)	8.9 (7.7-10.0)	3.5 (2.9-4.2)	11.1 (10.0-12.3)	16.2 (14.8-17.5)	28.4 (26.5-30.3)
	≥75	1.2 (0.7-1.7)	3.0 (2.3-3.7)	4.5 (3.6-5.4)	7.2 (6.1-8.4)	11.2 (9.8-12.5)	28.8 (26.9-30.7)	40.7 (38.6-42.8)	65.0 (62.7-67.4)

95%CI, 95% confidence interval; BCa, breast cancer; SPC, second primary cancer.

Supplementary Table 2. Sensitivity analyses defining **synchronous** second primary cancers as occurring within two months, six months and one year of a breast first primary cancer.

	Estimates according to the cut-off for defining synchronous SPC		
	2 months	6 months	1 year
Synchronous SPC [N (%)]			
All	215 (17.5%)	249 (20.3%)	287 (23.4%)
Stomach	6 (2.8%)	7 (2.8%)	9 (3.1%)
Colon	7 (3.3%)	12 (4.8%)	14 (4. %9)
Rectum	<3	<3	3 (1.0%)
Liver	<3	<3	<3
Lung	3 (1.4%)	3 (1.2%)	6 (2.1%)
Breast	177 (82.3%)	187 (75.1%)	193 (67.2%)
Cervix uteri	<3	<3	3 (1.0%)
Corpus uteri	<3	<3	7 (2.4%)
Ovary	<3	3 (1.2%)	3 (1.0%)
Kidney	<3	4 (1.6%)	6 (2.1%)
Bladder	<3	<3	<3
Thyroid	<3	4 (1.6%)	9 (3.1%)
Non-Hodgkin lymphoma	3 (1.4%)	7 (2.8%)	7 (2.4%)
Standardized incidence ratios of synchronous SPC^a (95%CI)			
All	13.57 (11.82-15.51)	5.30 (4.66-6.00)	3.06 (2.72-3.44)
Stomach	4.16 (1.53-9.05)	1.65 (0.66-3.39)	1.07 (0.49-2.03)
Colon	4.02 (1.62-8.29)	2.33 (1.20-4.07)	1.36 (0.75-2.29)
Rectum	--	--	0.64 (0.13-1.86)
Liver	--	--	--
Lung	4.72 (0.97-13.79)	1.59 (0.33-4.63)	1.58 (0.58-3.44)
Breast	39.92 (34.25-46.25)	14.21 (12.24-16.4)	7.36 (6.36-8.48)
Cervix uteri	--	--	0.85 (0.18-2.50)
Corpus uteri	--	--	1.64 (0.66-3.38)
Ovary	--	3.16 (0.65-9.23)	1.59 (0.33-4.66)
Kidney	--	5.92 (1.61-15.15)	4.41 (1.62-9.6')
Bladder	--	--	--
Thyroid	--	1.34 (0.36-3.43)	1.50 (0.69-2.84)
Non-Hodgkin lymphoma	5.74 (1.18-16.78)	4.51 (1.81-9.29)	2.26 (0.91-4.65)

95%CI, 95% confidence interval; SPC, second primary cancer; --, SIRs (95%CI) were not estimated as less than 3 SPCs were observed.

^a Stomach (C16), Colon (C18), Rectum (C19-C20), Liver and intrahepatic bile ducts (C22), Lung (including trachea and bronchus; C33-C34), Breast (C50), Cervix uteri (C53), Corpus uteri (C54), Ovary (C56), Kidney (C64), Bladder (C67), Thyroid (C73), Non-Hodgkin lymphoma (C82-C86, C96).

Supplementary Table 3. Sensitivity analyses defining **metachronous** second primary cancers as occurring two months, six months and one year after breast first primary cancer.

	Estimates according to the cut-off for defining metachronous SPC		
	2 months	6 months	1 year
Metachronous SPC [N (%)]	1014 (82.5%)	980 (79.7%)	942 (76.6%)
Cumulative incidence of metachronous SPC [% (95%CI)]			
At 1 year	0.6 (0.5-0.7)	0.6 (0.5-0.7)	0.8 (0.6-0.9)
At 3 years	2.0 (1.8-2.3)	2.1 (1.9-2.3)	2.2 (2.0-2.4)
At 5 years	3.3 (3.0-3.6)	3.3 (3.1-3.6)	3.5 (3.3-3.8)
At 10 years	6.6 (6.2-7.0)	6.7 (6.2-7.1)	7.0 (6.5-7.5)
Metachronous SPC^a [N (%)]			
Stomach	91 (9.0%)	90 (9.2%)	88 (9.3%)
Colon	137 (13.5%)	132 (13.5%)	130 (13.8%)
Rectum	44 (4.3%)	44 (4.5%)	43 (4.6%)
Liver	21 (2.1%)	21 (2.1%)	20 (2.1%)
Lung	84 (8.4%)	84 (8.6%)	81 (8.6%)
Breast	157 (15.5%)	147 (15.0%)	141 (15.0%)
Cervix uteri	23 (2.3%)	23 (2.3%)	21 (2.2%)
Corpus uteri	76 (7.5%)	76 (7.8%)	70 (7.2%)
Ovary	24 (2.4%)	23 (2.3%)	23 (2.4%)
Kidney	22 (2.2%)	19 (1.9%)	17 (1.8%)
Bladder	33 (3.3%)	33 (3.4%)	33 (3.5%)
Thyroid	78 (7.7%)	76 (7.8%)	71 (7.5%)
Non-Hodgkin lymphoma	42 (4.1%)	38 (3.9%)	38 (4.0%)
Standardized incidence ratios of metachronous SPC^a (95%CI)			
All	1.14 (1.07-1.21)	1.14 (1.07-1.21)	1.16 (1.09-1.23)
Stomach	1.23 (0.99-1.52)	1.27 (1.02-1.56)	1.32 (1.06-1.62)
Colon	1.38 (1.16-1.64)	1.38 (1.15-1.64)	1.44 (1.20-1.71)
Rectum	1.00 (0.73-1.34)	1.04 (0.75-1.39)	1.07 (0.78-1.44)
Liver	2.54 (1.57-3.89)	2.62 (1.62-4.01)	2.62 (1.60-4.05)
Lung	2.00 (1.59-2.47)	2.06 (1.64-2.55)	2.08 (1.65-2.59)
Breast	0.64 (0.55-0.75)	0.63 (0.53-0.74)	0.64 (0.53-0.75)
Cervix uteri	0.95 (0.60-1.43)	1.00 (0.64-1.50)	0.99 (0.61-1.51)
Corpus uteri	1.90 (1.50-2.38)	1.97 (1.56-2.47)	1.92 (1.50-2.43)
Ovary	1.47 (0.94-2.19)	1.47 (0.93-2.20)	1.56 (0.99-2.34)
Kidney	1.47 (0.92-2.23)	1.31 (0.79-2.05)	1.23 (0.72-1.97)
Bladder	1.51 (1.04-2.12)	1.57 (1.08-2.20)	1.66 (1.14-2.33)
Thyroid	1.30 (1.03-1.62)	1.31 (1.03-1.64)	1.29 (1.01-1.63)
Non-Hodgkin lymphoma	1.35 (0.98-1.83)	1.27 (0.90-1.74)	1.34 (0.95-1.83)

95%CI, 95% confidence interval; SPC, second primary cancer.

^a Stomach (C16), Colon (C18), Rectum (C19-C20), Liver and intrahepatic bile ducts (C22), Lung (including trachea and bronchus; C33-C34), Breast (C50), Cervix uteri (C53), Corpus uteri (C54), Ovary (C56), Kidney (C64), Bladder (C67), Thyroid (C73), Non-Hodgkin lymphoma (C82-C86, C96).

**The contribution of second primary cancers to the mortality of patients
with a breast first primary cancer**



The contribution of second primary cancers to the mortality of patients with a first primary breast cancer

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Abstract

Purpose Second primary cancers (SPCs) are estimated to affect nearly 5% of patients with breast cancer within 10 years of their diagnosis. This study aimed to estimate the contribution of SPCs to the mortality of patients with a breast first primary cancer (FPC).

Methods A population-based cohort of 17,210 patients with a breast FPC diagnosed between 2000 and 2010 was followed for SPCs (31/12/2015) and vital status (30/06/2021). Patients diagnosed with an SPC (265 synchronous and 897 metachronous, ≤ 1 and > 1 year after the FPC, respectively) were matched (1:3, by five-year age group and year of breast FPC diagnosis) to those without an SPC and alive when the corresponding SPC was diagnosed.

Results Significantly higher hazards of death were found among patients with an SPC [hazard ratio of 1.56, 95% confidence interval (CI) 1.29–1.89 for synchronous SPCs; and 2.85, 95%CI 2.56–3.17 for metachronous SPCs] compared to patients with a breast FPC only. Estimates were higher for synchronous lung, stomach, non-Hodgkin lymphoma and breast SPCs, and metachronous liver, stomach, ovary, lung, rectum, corpus uteri, colon, breast, and non-Hodgkin lymphoma SPCs. The 15-year cumulative mortality was 59.5% for synchronous SPCs and 68.7% for metachronous SPCs, which was higher than in patients with a breast FPC only (43.6% and 44.8%, respectively).

Conclusions In Northern Portugal, patients with an SPC following a breast FPC have a higher mortality compared with patients with a breast FPC only.

Keywords Breast neoplasms · Epidemiology · Population register · Mortality · Second primary neoplasm

Abbreviations

95%CI 95% Confidence interval
FPC First primary cancer

HR Hazards ratio
IACR International Association of Cancer Registries
IARC International Agency for Research on Cancer

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RD	Risk difference
RR	Relative risk
RORENO	North Region Cancer Registry of Portugal
SPC	Second primary cancer
USA	United States of America

Introduction

Breast cancer is the most incident cancer worldwide, accounting for 2.3 million new cancer cases in 2020. Further, the number of females living with a history of breast cancer in 2020 is estimated to be 7.8 million globally (five-year prevalence) [1, 2]. This occurs because of overall high survival, which reflects early diagnoses and improved therapies [3–5]. Survivors of breast cancer are at risk of adverse medical outcomes, such as subsequent primary cancers, mainly in the breast, endometrium, ovary, thyroid, lung, soft tissue sarcomas, leukemia, melanoma, and digestive organs [6]. Moreover, patients with a breast cancer share common risk factors, such as genetic, environmental, and hormonal, for a second primary cancer (SPC), and may suffer from side effects of cancer therapy [7–9].

The diagnosis of an SPC may be a major event among patients with a breast first primary cancer (FPC) [8]; in Europe, SPCs are diagnosed among nearly 5% of survivors of breast cancer within 10 years [10]. Previous studies have suggested that these patients, when diagnosed with an SPC, may have a worse prognosis compared to patients without an SPC [11–14]. However, the methodological framework related to the mortality of patients with an SPC is difficult, due to the contribution of each cancer to death, as well as other non-oncological causes of death [15]. Some studies have focused only on breast SPCs after a breast FPC or were incorporated in multi-cancer studies [11–14].

In Northern Portugal, breast cancer is the most incident cancer, accounting for nearly one third of female tumors and it is the first cause of cancer-related death [16, 17]. A previous study conducted in Northern Portugal evaluating SPCs after any FPC, found the prognosis of patients diagnosed with an SPC shortly after an FPC primarily depended on the type of FPC [18]. In contrast, for patients diagnosed with an SPC after a prolonged period following the initial FPC, survival outcomes were influenced by the specific site of the SPC. Considering the overall high survival from breast cancer, this study aims to extend previous observations of the incidence of multiple primary cancers in a cohort of patients with a breast cancer [19, 20], by estimating the contribution of an SPC to the mortality of patients with a breast FPC.

Methods

Study setting

A cohort of patients with breast cancer was retrieved from the North Region Cancer Registry (RORENO). This is a population-based cancer registry established in 1988 that covers Northern Portugal, representing over three million residents [16]. All incident cancers occurring in the catchment area of the registry are recorded, either by public or private hospitals and clinics, and private pathology laboratories. Registration follows the International Agency for Research on Cancer (IARC) rules, which include four dimensions: comparability, validity, timeliness and completeness [21]. The quality of the registry is maintained through routine screening with pre-defined algorithms for consistency and validity.

Definition of multiple primary cancers

Multiple primary cancers were defined as proposed by the International Association of Cancer Registries (IACR) and IARC [22]. Briefly, primary cancers are those that originally developed in an organ or tissue, not being an extension, recurrence, or metastasis. Different morphologies (even with the same topography) or dissimilar topographies should be regarded as multiple primary cancers, regardless of the time between diagnoses, unless they correspond to systemic cancers, which are considered the same cancer. Multiple primary cancers were defined as SPCs, when two primary cancers were diagnosed in the same individual, and third or higher order primary cancers when more than two primary cancers were registered.

Study design

All primary invasive tumors of the breast [International Statistical Classification of Diseases and Related Health Problems 10th Revision [23] (code C50)] diagnosed among female residents in Northern Portugal between 1 January 2000 and 31 December 2010 were identified ($n = 17,210$). Patients who had a previous cancer diagnosis other than skin non-melanoma ($n = 1064$) were excluded.

Vital status (death by any cause) was assessed through the National Health Service database, up to 30 June 2021, and subjects who could not be linked to the National Health Service database ($n = 165$) were excluded. The latter were not significantly different from included participants regarding age at diagnosis of the breast FPC [median

(percentile 25 – percentile 75): included – 57 (47–68) vs. excluded – 59 (48–76); $p = 0.058$].

The remaining patients ($n = 15,981$) were followed to 31 December 2015 to identify multiple primary cancers through record linkage with the list of cases registered by RORENO. Those diagnosed with third or higher order primary cancers ($n = 67$) were excluded [19]; thus, 1162 SPCs were available for the present study. SPCs were classified as synchronous when diagnosed within 12 months of the breast FPC ($n = 265$) or metachronous otherwise ($n = 897$), as previous studies on this topic [24].

Individuals with SPCs were matched 1:3 to individuals without SPCs who were alive when the corresponding SPC was diagnosed, by five-year age group (from 15–19 to 70–74, and ≥ 75) at breast FPC diagnosis and year of breast FPC diagnosis (Fig. 1).

Statistical analysis

For patients with a breast FPC who developed an SPC (FPC + SPC), survival time was considered as the time between SPC diagnosis and death from any cause or end of study period (30 June 2021), whichever occurred first. Survival time for patients with a breast FPC who did not develop an SPC (FPC only) was considered as the time between FPC diagnosis and death or end of study period, whichever occurred first, minus the time between the SPC

diagnosis and the FPC diagnosis of the matched FPC + SPC patient.

Cox-proportional hazards regression analyses were used to compute hazard ratios (HRs) for all-cause mortality adjusted for age (continuous) at breast FPC diagnosis with the corresponding 95% confidence intervals (CIs). The proportional hazards assumption was evaluated using Schoenfeld residuals.

The observed cumulative mortality was estimated using 1 – Kaplan–Meier [25]. The relative risk (RR) and risk difference (RD) of observed cumulative mortality were estimated for the comparison between patients with FPC + SPC, and those with an FPC only.

Several sensitivity analyses were performed defining SPCs as diagnosed two and six months after the breast FPC, as well as between two and twelve months following the breast FPC.

Data analysis was conducted using the statistical program Stata (Version 15.1, StataCorp, College Station, Texas). Results were considered statistically significant for p -value < 0.05 .

Results

A total of 1162 patients with a breast FPC + SPC and 3486 patients with a breast FPC only were included (Fig. 1). The most common SPC sites were breast, digestive organs,

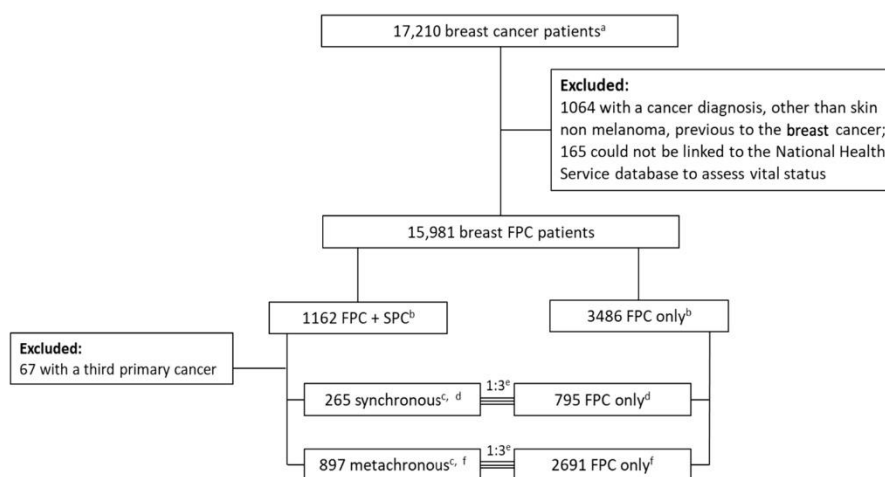


Fig. 1 Flowchart of patient inclusion in the study. *FPC* first primary cancer, *SPC* second primary cancer. ^aDiagnosed between 1 January 2000 and 31 December 2010. ^bFollow-up to 30 June 2021. ^cSynchronous when diagnosed within 12 months of the breast FPC and metachronous, otherwise; follow-up to 31 December 2015. ^dThe median (percentile 25—percentile 75) age at diagnosis of FPC was 61 (49–72) for synchronous SPC and 62 (49–73) for the corresponding FPC only patients. ^eMatched 1:3 by five-year age group (from 15–19

to 70–74, and ≥ 75) at breast FPC diagnosis, year of breast FPC diagnosis (single year for 1157 SPCs, and grouped years for 5 cases, as insufficient matches were made using a single year) and being alive when the corresponding SPC was diagnosed. ^fThe median (percentile 25—percentile 75) age at diagnosis of FPC was 60 (50–70) for metachronous SPC and 60 (50–70) for the corresponding FPC only patients

Table 1 Observed deaths up to 30 June 2021 among first primary breast cancer patients and respective hazard ratios, according to site of synchronous or metachronous second primary cancer diagnosis

	Total N	Deaths N (%)	Adjusted HR ^a (95%CI)
Synchronous SPCs			
FPC only	795	343 (43.1)	1
FPC + SPC ^b	265	153 (57.7)	1.56 (1.29–1.89)
Stomach	9	8 (88.9)	7.28 (2.83–18.73)
Colon	13	10 (76.9)	1.41 (0.66–3.00)
Lung	6	5 (83.33)	7.72 (1.89–31.57)
Breast	178	88 (49.4)	1.28 (1.00–1.64)
Corpus uteri	6	4 (66.7)	0.52 (0.11–2.31)
Kidney	5	1 (20.0)	0.49 (0.06–4.24)
Thyroid	9	4 (44.4)	1.21 (0.38–3.81)
Non-Hodgkin lymphoma	6	6 (100.0)	2.97 (1.06–8.28)
Other SPCs ^c	33	27 (81.8)	2.57 (1.61–4.12)
Metachronous SPCs			
FPC only	2691	899 (33.3)	1
FPC + SPC ^b	897	544 (60.6)	2.85 (2.56–3.17)
Stomach	85	67 (78.8)	6.52 (4.63–9.19)
Colon	110	64 (58.2)	2.01 (1.49–2.71)
Rectum	39	22 (56.4)	2.59 (1.52–4.40)
Liver	21	20 (95.2)	13.10 (6.26–27.43)
Lung	79	64 (81.1)	6.01 (4.31–8.61)
Breast	137	57 (41.6)	1.97 (1.42–2.72)
Cervix uteri	20	8 (40.0)	1.09 (0.49–2.43)
Corpus uteri	68	37 (54.4)	2.21 (1.48–3.29)
Ovary	23	18 (57.7)	6.28 (3.16–12.45)
Bladder	33	19 (57.6)	1.15 (0.68–1.93)
Thyroid	71	20 (28.2)	1.04 (0.63–1.74)
Non-Hodgkin lymphoma	38	21 (55.3)	1.88 (1.10–3.21)
Other SPCs ^d	173	127 (73.4)	4.53 (3.58–5.74)

CI confidence interval, FPC first primary cancer, HR hazard ratio, SPC second primary cancer

Only shown for synchronous SPC sites with at least five cases and metachronous SPC sites with at least 20 cases

^aAdjusted for age (continuous) at breast FPC diagnosis

^bStomach (C16), Colon (C18), Rectum (C19–C20), Liver and intrahepatic bile ducts (C22), Lung (including trachea and bronchus, C33–C34), Breast (C50), Cervix uteri (C53), Corpus uteri (C54), Ovary (C56), Kidney (C64), Bladder (C67), Thyroid (C73), Non-Hodgkin lymphoma (C85) defined according to the International Statistical Classification of Diseases and Related Health Problems 10th Revision [23]

^cOther synchronous SPC sites include: Lip, oral cavity and pharynx (C00–C14), Small intestine (C17), Rectum (C19–C20), Anus and anal canal (C21), Liver and intrahepatic bile ducts (C22), Gallbladder (C23), Pancreas (C25), Nasal cavity and middle ear (C30), Melanoma of skin (C43), Vulva (C51), Cervix uteri (C53), Uterus, part unspecified (C55), Ovary (C56), Renal pelvis (C65), Ureter (C66), Bladder (C67), Without specification of site (C80), Malignant immunoproliferative diseases (C88), Multiple myeloma and malignant plasma cell neoplasms (C90), Lymphoid leukaemia (C91), Myelodysplastic syndromes (D46) defined according to the International Statistical Classification of Diseases and Related Health Problems 10th Revision [23]

Table 1 (continued)

erative diseases (C88), Multiple myeloma and malignant plasma cell neoplasms (C90), Lymphoid leukaemia (C91), Myelodysplastic syndromes (D46) defined according to the International Statistical Classification of Diseases and Related Health Problems 10th Revision [23]

^dOther synchronous SPC sites include: Lip, oral cavity and pharynx (C00–C14), Oesophagus (C15), Small intestine (C17), Anus and anal canal (C21), Gallbladder (C23), Pancreas (C25), Nasal cavity and middle ear (C30), Larynx (C32), Thymus (C37), Bone and articular cartilage of limbs (C40), Melanoma of skin (C43), Mesothelioma (C45), Kaposi sarcoma (C46), Peripheral nerves and autonomic nervous system (C47), Vulva (C51), Vagina (C52), Uterus, part unspecified (C55), Kidney (C64), Meninges (C70), Adrenal gland (C74), Without specification of site (C80), Hodgkin lymphoma (C81), Malignant immunoproliferative diseases (C88), Multiple myeloma and malignant plasma cell neoplasms (C90), Lymphoid leukaemia (C91), Myeloid leukaemia (C92–C94), Leukaemia of unspecified cell type (C95), Myelodysplastic syndromes (D46), Other neoplasms of uncertain or unknown behaviour of lymphoid, haematopoietic and related tissue (D47) defined according to the International Statistical Classification of Diseases and Related Health Problems 10th Revision [23]

thyroid, lung, and corpus uteri (Table 1). During follow-up, a total of 1242 deaths (35.6%) were reported among patients with a breast FPC only, whereas 697 (60.0%) deaths were reported among patients with an FPC + SPC. Overall, patients with a synchronous or metachronous SPC had a significantly higher hazard of death compared to patients with a breast FPC only [HR = 1.56 (95%CI 1.29–1.89) and HR = 2.85 (95%CI 2.56–3.17), respectively]. Statistically significant HRs were observed for lung, stomach, non-Hodgkin lymphoma and breast synchronous SPCs, with HRs ranging from 1.28 (95%CI 1.00–1.64) to 7.72 (95%CI 1.89–31.57). For patients diagnosed with a metachronous SPC, liver, stomach, ovary, lung, rectum, corpus uteri, colon, breast, and non-Hodgkin lymphoma had statistically significant HRs, with estimates ranging from 1.88 (95%CI 1.10–3.21) to 13.10 (95%CI 6.26–27.43).

The cumulative mortality of patients with a breast FPC only and those with an FPC + SPC is shown in Table 2 and Fig. 2. The 15-year cumulative mortality was 59.5% (95%CI 57.6–61.45) for patients with an FPC + synchronous SPC and 43.6% (95%CI 41.7–45.5) for patients with a breast FPC only, with an RD of 15.9%. A gradual decrease in the RR from 2.79 at one-year to 1.36 at 15-years was observed. The cumulative mortality at 15-years was 68.7% (95%CI 66.7–70.6) for patients with an FPC + metachronous SPC versus 44.8% (95%CI 42.9–46.7) for patients with a breast FPC only, with an RD of 23.9%. The RR ranged from 5.81 at one-year to 1.53 at 15-years.

Analyses defining synchronous SPCs as occurring within two and six months of a breast FPC generally resulted in lower HR estimates (Supplementary Table 1). The HR was 1.46 (95%CI 1.16–1.83) for synchronous

Table 2 Observed cumulative mortality^a of first primary breast cancer patients with and without a synchronous or metachronous second primary cancer diagnosis

Time since SPC, years	FPC only Cumulative mortality % (95%CI)	FPC + SPC Cumulative mortality % (95%CI)	RR ^b	RD ^c %
Synchronous SPCs				
1	3.9 (3.1–4.7)	10.9 (10.1–11.7)	2.79	7.00
3	13.6 (12.5–14.7)	25.7 (24.5–26.8)	1.89	12.10
5	20.7 (19.5–22.0)	35.1 (33.9–36.3)	1.70	14.40
10	33.1 (31.7–34.6)	46.4 (44.9–47.9)	1.40	13.30
15	43.6 (41.7–45.5)	59.5 (57.6–61.45)	1.36	15.90
Metachronous SPCs				
1	4.3 (3.5–5.1)	25.0 (24.2–25.9)	5.81	20.70
3	11.3 (10.2–12.4)	40.8 (39.7–41.9)	3.61	29.50
5	17.5 (16.2–18.7)	47.7 (46.5–49.0)	2.73	30.20
10	32.3 (30.8–33.8)	61.1 (59.6–62.5)	1.89	28.80
15	44.8 (42.9–46.7)	68.7 (66.7–70.6)	1.53	23.90

CI confidence interval, FPC first primary cancer, RD risk difference, RR relative risk, SPC second primary cancer

^aCalculated using 1 – Kaplan–Meier [25]

^bCalculated as observed mortality in FPC + SPC / observed mortality in FPC only

^cCalculated as observed mortality FPC + SPC – observed mortality in FPC only

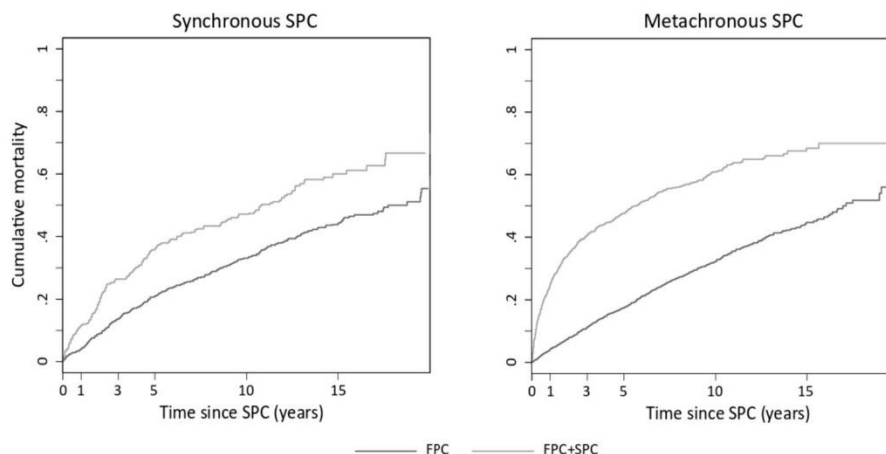


Fig. 2 Observed cumulative mortality^a of breast first primary cancer patients with and without a synchronous or metachronous second primary cancer diagnosis. FPC first primary cancer, SPC second primary cancer. ^aCalculated using 1 – Kaplan–Meier [25]

SPCs diagnosed within two months of the breast FPC, 1.84 (95%CI 1.29–2.64) for SPCs diagnosed between two and 12 months after the breast FPC, and 2.71 (95%CI 2.45–3.02) for metachronous SPCs diagnosed more than 12 months after the breast FPC. When using the cut-off of six months to define synchronous and metachronous SPCs, the HRs were 1.51 (95%CI 1.23–1.86) for synchronous SPCs and 2.77 (95%CI 2.49–3.07) for metachronous SPCs.

The sensitivity analyses for cumulative mortality, using the two- or six-months cut-off to define synchronous and metachronous SPCs, yielded lower estimates for patients diagnosed with an SPC within two months of the breast FPC. No differences in cumulative mortality were observed for metachronous SPCs using the different time cut-offs (Supplementary Table 2).

Discussion

Our population-based cohort study showed that patients with a breast FPC diagnosed with an SPC had a higher hazard of death of 1.5-fold for synchronous SPCs and almost three-fold for metachronous SPCs compared with patients with a breast FPC only. The sites with higher HRs were similar for synchronous and metachronous SPCs, namely lung, stomach, breast, non-Hodgkin lymphoma, liver, genital, and colon and rectum. Overall, the cumulative mortality estimates were higher for patients with a synchronous or metachronous SPC compared to patients with a breast FPC only.

Previous research has described a higher mortality among patients with an SPC compared to patients with a breast FPC only [11–14]. Deng and colleagues published data from a large cohort including over 60 thousand women with breast cancer from the USA, using the Surveillance, Epidemiology, and End Results, diagnosed between 2000 to 2016, with an average follow-up time of 42 months [14]. They found that patients with any SPC diagnosed more than six months after the FPC had an HR of death of 1.18 compared to patients with a breast cancer only. The SPC sites with higher HRs were breast, lung, colon, rectum, uterus, lymphoma, melanoma, thyroid, and leukemia [14], which is in line with our findings. Their 15-year cumulative mortality estimates were 67.5% for patients with an SPC and 60.4% for patients with an FPC only [14]. Many previous studies have considered breast cancer as the FPC and/or SPC [12, 13, 26]. A systematic review by Pan and colleagues included 15 relevant studies, with patients with unilateral breast cancer only and patients with bilateral breast cancer. They compared the HRs of death among those with a unilateral breast cancer and a bilateral breast cancer, combining different definitions for synchronous and a metachronous within three, six and 12 months as the cut-off time. Compared to patients with a unilateral breast cancer only, they estimated an HR of 1.68 for bilateral breast cancer, 2.01 for synchronous breast SPC and 3.22 for a metachronous breast SPC [12]. Using data from the Danish Breast Cancer Cooperative Group database, Langballe and colleagues studied nearly 70 thousand women with breast cancer diagnosed between 1978 and 2012, and followed until 2015 for cancer-specific death. Compared to patients with a unilateral breast FPC, those with a bilateral breast cancer had a two-fold higher hazard of death [13].

We found that patients with synchronous and metachronous SPCs both have a higher mortality compared to patients with a breast FPC only, though mortality was lower among those with synchronous SPCs. Patients diagnosed with synchronous SPCs may be under closer

medical monitoring due to their breast FPC being more recently diagnosed. Consequently, there is a possibility that a subsequent SPC is detected at an earlier stage and given the closer medical surveillance, prompt initiation of treatment may contribute to their lower mortality compared to those with metachronous SPCs. Conversely, patients diagnosed with metachronous SPCs might be detected at later stages or be associated with more aggressive tumor characteristics, resulting in an even worse prognosis among these patients. A previous systematic review described above by Pan and colleagues estimated higher HR for synchronous breast SPC and metachronous breast SPC compared to patients with a unilateral breast cancer only [12]. Moreover, a study by Pacheco-Figueiredo and colleagues reported that the survival of patients with metachronous SPCs may be more influenced by the site of the SPC whereas in patients with synchronous SPCs, survival varied considering the site of the FPC [18]. In the current study, we may hypothesize that the breast FPC is contributing to the higher survival observed among patients with a synchronous SPC.

Strengths and limitations

Our data was collected from a population-based registry, RORENO, which is highly representative of patients with breast cancer from Northern Portugal. It has a large catchment area, integrating public and private institutions involved in the diagnosis and care of patients with cancer; and has a long-term and complete follow-up with only 1% losses identified. Furthermore, we provide sensitivity analyses considering the cut-off for defining synchronous and metachronous SPCs at two and six months. However, some limitations should be discussed. Patients were followed for the occurrence of an SPC until 2015, which was the maximum data available from RORENO at the time of the study. This allowed a minimum follow-up of five years and a maximum follow-up of 15 years. Although we would likely have a larger number of patients with metachronous SPCs if there was a longer follow-up to identify multiple primary cancers, we do not believe that the results of our study would be any different. In the present work, we are assuming, that all other causes of death, besides cancer related death, influence the survival of patients with an FPC only or an FPC + SPC in a similar manner. However, HRs will inherently be influenced by the timing of SPC diagnoses relative to the FPC, while synchronous SPCs occur almost concurrently with the FPC. Nevertheless, our study considers the FPC and SPC by calculating survival time for all patients from the moment the SPC is diagnosed, irrespective of whether they had an SPC or not, to ensure that patients with FPCs only have at least the same duration of survival until the occurrence of the SPC of the matched patient. This is necessary because the

effect measures will be influenced by the SPC time from the first primary to the second primary. Some site-specific HRs may lack the statistical power needed for robust interpretation on an individual basis, particularly for SPCs with small sample sizes or low event rates, these estimates should be interpreted with caution. Information on clinical data that could influence the prognosis of patients with a breast cancer was not available, namely stage at FPC and SPC diagnosis, hormonal receptor status of the tumor, treatment regime, as well as menopausal status, family history or genetic susceptibility. Previous studies have shown that lifestyle risk factors, such as obesity, tobacco, treatment side-effects, or even modified standard therapy may impact the survival of patients with multiple cancers [12, 14, 23, 27].

Conclusion

This is the first comprehensive analysis in Northern Portugal evaluating the impact of breast cancer, which is the most incident cancer worldwide and in Portugal, on SPC survivorship. We found patients with an SPC following a breast FPC have a higher mortality than those with a breast FPC only and mortality was higher for those with a metachronous SPC. Lung, stomach, breast, non-Hodgkin lymphoma, liver, genital, and colon and rectum were SPC sites with the worst prognosis. These findings highlight the need for surveillance of patients with a breast cancer and management of the expectations of these patients.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s10549-024-07361-3>.

Author contributions All authors contributed to the study conception and design. Data preparation and collection were performed by Elisabete Gonçalves, Jéssica Rocha Rodrigues, Rita Calisto, Maria José Bento, and Samantha Morais. Analyses were performed by Elisabete Gonçalves and Samantha Morais. The first draft of the manuscript was written by Elisabete Gonçalves, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

Declarations

Competing interests The authors have no relevant financial or non-financial interests to disclose.

Data availability The data that support the findings of this study are available from the North Region Cancer Registry (RORENO), but restrictions apply to the availability of these data, which were used under license for the current study and so are not publicly available. Data may be available from the authors upon reasonable request and with permission of RORENO.

Ethical approval The study was approved by the Ethics Committee of the Portuguese Institute of Oncology of Porto (Ref. CES IPO: 332/020) and the analyses were performed according to RORENO guidelines ensuring the anonymity of information used.

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Supplementary Table 1. Observed deaths up to 30 June 2021 among first primary breast cancer patients and respective hazard ratios, according to site of synchronous or metachronous second primary cancer diagnosis considering different periods of cut-off to define second primary cancers.

		Total N	Deaths N (%)	Adjusted HR ^a (95%CI)
Two months				
Synchronous SPCs (within two months of the FPC)	FPC only	600	250 (41.7)	1
	FPC+SPC ^b	200	108 (54.0)	1.46 (1.16-1.83)
	Stomach	6	6 (100.0)	161.76 (12.61-2075.71)
	Colon	7	6 (85.7)	1.67 (0.59-4.69)
	Lung	3	2 (66.7)	3.15 (0.45-22.05)
	Breast	164	79 (48.2)	1.25 (0.96-1.63)
	Corpus uteri	0	--	--
	Kidney	1	0 (0.0)	--
	Thyroid	2	1 (50.0)	2.20 (0.13-38.52)
	Non-Hodgkin lymphoma	3	3 (100.0)	3.71 (0.71-19.23)
	Other SPCs	14	11 (78.6)	2.62 (1.23-1.10)
Metachronous SPCs (between two and twelve months after the FPC)	FPC only	195	93 (47.7)	1
	FPC+SPC ^b	65	45 (69.2)	1.84 (1.29-2.64)
	Stomach	3	2 (66.7)	4.27 (0.64-28.54)
	Colon	6	4 (66.7)	1.78 (0.53-5.95)
	Rectum	1	1 (100.0)	--
	Liver	0	--	--
	Lung	3	3 (100.0)	--
	Breast	14	9 (64.3)	1.80 (0.81-3.99)
	Cervix uteri	1	0 (0.0)	--
	Corpus uteri	6	4 (66.7)	0.51 (0.11-2.31)
	Ovary	1	1 (100.0)	--
	Bladder	1	1 (100.0)	--
	Thyroid	7	3 (42.9)	1.17 (0.31-4.47)
	Non-Hodgkin lymphoma	3	3 (100.0)	6.87 (0.51-93.01)
	Other SPCs	19	14 (73.7)	2.41 (1.25-4.61)
Metachronous SPCs (more than two months after the FPC)	FPC only	2886	992 (34.4)	1
	FPC+SPC ^b	962	589 (61.2)	2.71 (2.45-3.02)
	Stomach	88	69 (78.4)	5.83 (4.20-8.10)
	Colon	116	68 (58.6)	1.91 (1.43-2.55)
	Rectum	40	23 (57.5)	2.65 (1.57-4.45)
	Liver	21	20 (95.2)	13.10 (6.26-27.43)
	Lung	82	67 (81.7)	6.17 (4.39-8.68)
	Breast	151	66 (43.7)	1.93 (1.43-2.60)
	Cervix uteri	21	8 (38.1)	1.07 (0.48-2.40)
	Corpus uteri	74	41 (55.4)	1.93 (1.32-2.83)
	Ovary	24	19 (79.2)	6.63 (3.39-12.96)
	Bladder	33	19 (79.2)	1.15 (0.68-1.93)
	Thyroid	78	23 (29.5)	1.06 (0.66-1.71)
	Non-Hodgkin lymphoma	41	24 (58.5)	2.00 (1.21-3.29)
	Other SPCs	193	142 (73.4)	3.98 (3.19-4.95)
Six months				
Synchronous SPCs (within six months of the FPC)	FPC only	690	300 (43.5)	1
	FPC+SPC ^b	230	129 (56.1)	1.51 (1.23-1.86)
	Stomach	7	6 (85.7)	6.39 (2.17-18.78)
	Colon	11	10 (90.9)	1.97 (0.90-4.32)
	Lung	3	2 (66.7)	3.14 (0.45-22.05)
	Breast	172	84 (48.8)	1.25 (0.97-1.62)
	Corpus uteri	0	--	--
	Kidney	4	1 (25.0)	0.62 (0.07-5.57)
	Thyroid	4	1 (25.0)	0.93 (0.10-8.79)
	Non-Hodgkin lymphoma	6	6 (100.0)	2.97 (1.06-8.28)
	Other SPCs	23	19 (82.6)	2.83 (1.61-4.96)

	FPC only			1
	FPC+SPC ^b	932	568 (60.9)	2.77 (2.49-3.07)
	Stomach	87	69 (79.3)	6.58 (4.70-9.22)
	Colon	112	64 (57.1)	1.88 (1.39-2.53)
	Rectum	40	23 (57.5)	2.65 (1.57-4.45)
	Liver	21	20 (95.2)	13.10 (6.26-27.43)
	Lung	82	67 (81.7)	6.17 (4.39-8.68)
	Breast	143	61 (42.7)	1.98 (1.44-2.70)
	Cervix uteri	21	8 (38.1)	1.07 (0.48-2.40)
	Corpus uteri	74	41 (55.4)	1.93 (1.32-2.83)
	Ovary	23	18 (78.3)	6.28 (3.16-12.45)
	Bladder	33	19 (57.6)	1.15 (0.68-1.93)
	Thyroid	76	23 (30.3)	1.09 (0.68-1.76)
	Non-Hodgkin lymphoma	38	21 (55.3)	1.88 (1.10-3.21)
	Other SPCs	182	134 (73.6)	4.24 (3.37-5.32)

CI, confidence interval; FPC, first primary cancer; HR, hazard ratio; NA, not applicable; SPC, second primary cancer.

^a Adjusted for age (continuous).

^b Stomach (C16), Colon (C18), Rectum (C19-C20), Liver and intrahepatic bile ducts (C22), Lung (including trachea and bronchus, C33-C34), Breast (C50), Cervix uteri (C53), Corpus uteri (C54), Ovary (C56), Kidney (C64), Bladder (C67), Thyroid (C73), Non-Hodgkin lymphoma (C85) defined according to the International Statistical Classification of Diseases and Related Health Problems, 10th Revision [23].

Supplementary Table 2. Observed cumulative mortality^a of first primary breast cancer patients with and without a synchronous or metachronous second primary cancer diagnosis considering different periods of cut-off to define second primary cancers.

		FPC only	FPC+SPC		
	Time since SPC, years	Cumulative mortality % (95%CI)	Cumulative mortality % (95%CI)	RR ^b	RD ^c %
Two months					
Synchronous SPCs (within two months of the FPC)	1	3.8 (3.0-4.6)	8.5 (7.8-9.3)	2.24	4.70
			21.5 (20.4-22.6-	1.54	7.50
	3	14.0 (12.9-15.1)	22.6)		
	5	20.5 (19.3-21.7)	30.5 (29.3-31.7)	1.49	10.00
	10	31.8 (30.35-33.3)	42.5 (41.0-44.0)	1.34	10.70
	15	41.58 (39.7-43.51)	55.1 (53.2-57.1)	1.33	13.60
Metachronous SPCs (between two and twelve months after the FPC)	1	4.1 (3.3-4.9)	18.5 (17.7-19.2)	4.51	14.40
	3	12.3 (11.2-13.4)	38.5 (37.4-39.6)	3.13	26.20
	5	21.5 (20.3-22.8)	49.2 (48.0-50.5)	2.29	27.70
	10	36.9 (35.5-38.4)	58.5 (57.0-59.9)	1.59	21.60
	15	50.5 (48.7-52.4)	73.1 (71.3-75.0)	1.45	22.60
Metachronous SPCs (more than two months after the FPC)	1	4.3 (3.5-5.1)	24.6 (23.8-25.4)	5.72	20.30
	3	11.4 (10.3-12.5)	40.6 (39.5-41.7)	3.56	29.20
	5	17.7 (16.5-19.0)	47.8 (46.6-49.1)	2.70	30.10
	10	32.6 (31.2-34.1)	60.8 (59.3-62.3)	1.87	28.20
	15	45.3 (43.4-47.3)	69.7 (67.8-71.7)	1.54	24.40
Six months					
Synchronous SPCs (within six months of the FPC)	1	4.1 (3.2-4.9)	10.4 (9.7-11.2)	2.54	6.30
	3	14.1 (12.9-15.2)	24.3 (23.2-25.4)	1.72	10.20
	5	20.7 (19.5-22.0)	33.9 (32.7-35.1)	1.64	13.20
	10	33.2 (31.7-34.7)	46.1 (44.6-47.5)	1.39	12.90
	15	43.6 (41.7-45.5)	57.4 (55.5-59.3)	1.32	13.80
Metachronous SPCs (more than six months after the FPC)	1	4.2 (3.4-5.0)	24.6 (23.8-25.4)	5.86	20.40
	3	11.3 (10.2-12.4)	40.5 (39.4-41.6)	3.58	29.20
	5	17.6 (16.4-18.8)	47.6 (46.3-48.8)	2.70	30.00
	10	32.3 (30.8-33.7)	60.5 (59.0-62.0)	1.87	28.20
	15	44.7 (42.7-46.6)	69.8 (67.9-71.8)	1.56	25.10

CI, confidence interval; FPC, first primary cancer; RD, relative difference; RR, relative risk; SPC, second primary cancer.

^a Calculated using 1 – Kaplan-Meier [25].

^b Calculated as observed mortality in FPC+SPC / observed mortality in FPC only.

^c Calculate as observed mortality FPC+SPC – observed mortality in FPC only.

Risk and survival of third primary cancers in a population-based cohort of breast cancer patients

Risk and Survival of Third Primary Cancers in a Population-Based Cohort of Breast Cancer Patients

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Keywords

Epidemiology · Mortality · Multiple primary neoplasms · Registries · Breast neoplasms

Abstract

Introduction: The growing number of women diagnosed with breast cancer (BCa) together with high survival has resulted in an increasing population of survivors at risk of subsequent primary cancers. This study aimed to estimate the long-term risk and survival of third primary cancers (TPCs) among females with a first primary BCa. **Methods:** Breast first primary cancers (FPCs) from the Portuguese North Region Cancer Registry, diagnosed between 2000 and 2010 ($n = 15,981$), were followed for a TPC (December 31, 2015) and death from any cause (June 30, 2021). The cumulative incidence of and mortality among TPCs were estimated. To compare survival, female patients with a TPC were matched (1:1, by age group, years between FPC and second primary cancer [SPC] diagnosis, and SPC location) to FPC + SPC patients without a TPC. **Results:** Overall, 67 (0.4% of FPCs and 5.4% of SPCs) TPCs were diagnosed. The most common TPC sites were digestive, breast, and female genital organs. Among all FPCs, the 15-year cumulative incidence (95% confidence interval [CI]) of a TPC was 0.69% (0.47–0.90%) and among SPCs,

7.21% (4.99–9.43%). The 15-year cumulative mortality of TPCs and matched patients was 70.0% and 51.5%, respectively. For TPCs, compared to matched SPC only patients, the age-adjusted hazard ratio (95% CI) for death was 2.86 (1.61–5.07). **Discussion/Conclusion:** The most common TPC sites were digestive, breast, and female genital organs, with a 15-year cumulative incidence of 0.69% among FPCs. TPCs had a worse long-term survival compared to patients with an SPC only.

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Introduction

Breast cancer (BCa) is the most common malignancy diagnosed worldwide, accounting for 7.8 million women alive who were diagnosed with BCa in the past five years, and the second leading cause of death from cancer [1]. The survival of patients with BCa has increased in the last decades [2] due to improved access to early diagnosis [3] and effective treatments, including new adjuvant drugs and less aggressive surgeries [4], leading to a growing number of BCa survivors. These patients have been shown to be at increased risk for subsequent primary cancers at several sites due to shared etiology, including ge-

netic susceptibility and environmental factors, as well as treatment effects [5, 6]. Previous studies have described the epidemiological and clinical characteristics of BCa patients with second primary cancers (SPCs) [7–9], as well as the occurrence of third primary cancers (TPCs) of nonbreast origin among women with bilateral BCa [10]. Nevertheless, there is a lack of published data addressing the risk and survival of BCa patients with higher order primary cancers. Therefore, considering that BCa is the most frequent malignancy in Northern Portugal [11] and responsible for the highest proportion of SPCs among females [12], this study aimed to estimate the long-term risk and survival of TPCs among patients with a breast first primary cancer (FPC).

Methods

A population-based cohort of female breast (International Statistical Classification of Diseases and Related Health Problems 10th Revision C50 [13]) FPCs ($n = 15,981$) from the North Region Cancer Registry of Portugal (RORENO) diagnosed in 2000–2010 was followed for the diagnosis of multiple primary cancers (MPCs; December 31, 2015) and vital status (June 30, 2021). MPCs were defined as proposed by the International Association of Cancer Registries and International Agency for Research on Cancer [14]. These were considered SPCs ($n = 1,229$), TPCs ($n = 67$), and fourth or higher order primary cancers ($n = 4$) when two, three, or more than three primary cancers, respectively, were diagnosed in the same individual.

Cumulative incidence and corresponding 95% confidence intervals (CIs) for the occurrence of TPCs considering the date of diagnosis of the breast FPC and of the SPC were estimated separately, accounting for the competing event of death [15]. The maximum possible follow-up time from FPC to TPC and from SPC to TPC was 15 years.

A matched-sample analysis was conducted to estimate the survival of TPCs; patients diagnosed with more than three primary cancers ($n = 4$) were excluded. Females with TPCs (SPC + TPC) were matched 1:1 to females with an SPC but without a TPC (SPC only) who were alive when the corresponding TPC was diagnosed, by age-group (<45, 45–54, 55–64, 65–74, and ≥ 75 for 39 matches; <45, 45–64, and ≥ 65 for 21 matches; <65 and ≥ 65 for three matches), number of years between FPC and SPC diagnoses (single year [from 1 to 15 years] for 49 matches; first-year and then two-year groups [from 2–3 years to 14–15 years] for four matches; and three-year groups [from 1–3 years to 13–15 years] for 10 matches), and SPC location (SPC site for 56 matches; SPC group: digestive organs [C15–C26]; respiratory and intrathoracic organs [C30–C39]; skin melanoma [C43]; breast [C50]; female genital organs [C51–C58]; urinary tract [C64–C68]; eye [C69]; brain and other parts of central nervous system [C70–C72]; lymphoid, hematopoietic, and related tissue [C81–C96]; uncertain or unknown behavior [D37–D48] [13] for seven matches).

Survival time for patients with a TPC was considered as the time between TPC diagnosis and death from any cause or end of study follow-up (June 30, 2021), whichever occurred first. For SPC only patients, survival time was considered as the time between SPC diagnosis and death or end of study follow-up (June 30, 2021), whichever occurred first, minus the time between the SPC diagnosis and the TPC diagnosis of the matched patients with TPC. The

maximum possible vital status follow-up time for SPC only patients (from SPC diagnosis) was 21 years and for SPC + TPC patients (from TPC diagnosis) was 18 years.

Cox proportional hazards regression analyses were used to compute hazard ratios for all-cause mortality adjusted for age (continuous) with the corresponding 95% CI. The proportional hazards assumption was evaluated using Schoenfeld residuals. The observed cumulative all-cause mortality was estimated using 1 – Kaplan-Meier [16]. Statistical analyses were conducted using Stata[®], version 15.1 (StataCorp., College Station, TX, USA).

Results

During follow-up to the end of 2015, 1,229 patients developed a subsequent primary cancer (7.7% of breast FPCs) and 67 patients a TPC (0.4% of breast FPCs and 5.4% of FPC + SPC; Table 1). A total of 56 contralateral BCas were diagnosed among patients without a TPC ($n = 1,162$), while one contralateral second primary BCa was observed in patients with a TPC ($n = 67$). The median (percentile 25–percentile 75 [P25–P75]) age at breast FPC diagnosis was 57 (47–68) years. For patients diagnosed with an SPC only, the median (P25–P75) time between the FPC and the SPC was 4.0 (1.2–7.3) years; the corresponding time for patients with a TPC was 3.6 (1.0–6.4) years. The median (P25–P75) time between an SPC and a TPC was 0.6 (0.2–1.9) years.

Among the 67 females diagnosed with a TPC, over one-third of TPCs (34.3%, $n = 23$) occurred in digestive organs, and nearly half (46.3%, $n = 31$) of TPCs occurred in patients with a previous digestive SPC (Fig. 1; online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000522057). Breast and female genital organs were also common TPC sites, occurring in 6 (8.9%) and 11 (16.4%) females, respectively, as well as an SPC among females diagnosed with a TPC, accounting for 19.4% ($n = 13$) and 13.4% ($n = 9$) of cases, respectively.

The 10- and 15-year cumulative incidences (95% CI) of a TPC were 0.42% (0.31–0.54%) and 0.69% (0.47–0.90%), respectively, among patients with a breast FPC (Fig. 2a). Among patients with an SPC following a breast FPC, the 10-year cumulative incidence (95% CI) of a TPC was 7.21% (4.99–9.43%; Fig. 2b).

The five-year cumulative all-cause mortality (95% CI) of the SPC + TPC patients and matched SPC-only patients was 57.1% (47.6–66.6%) and 29.1% (19.5–38.7%), respectively, whereas the corresponding risk of mortality at 10 years was 70.0% (60.0–80.0%) and 43.4% (33.3–53.5%; Fig. 3). For SPC + TPC patients, compared to matched SPC only patients, the crude and age-adjusted hazard ratios (95% CI) for death were 2.43 (1.39–4.27) and 2.86 (1.61–5.07), respectively.

Table 1. Characteristics of female breast FPC patients with and without a subsequent primary cancer

N (%)	Total 15,981 (100.0)	Patients without a subsequent primary 14,752 (92.3)	Patients with a subsequent primary 1,229 (7.7)	
			Patients without a TPC 1,162 (93.2)	Patients with a TPC 67 (5.4 of SPCs; 0.4 of FPCs)
Age at diagnosis of BCa (median [P25–P75]), years	57 (47–68)	56 (47–68)	60 (50–70)	62 (54–74)
<45	3,032 (19.0)	2,879 (19.5)	146 (12.6)	7 (10.4)
45–54	4,162 (26.0)	3,874 (26.3)	278 (23.9)	10 (14.9)
55–64	3,565 (22.3)	3,267 (22.1)	276 (23.7)	22 (32.8)
65–74	2,274 (14.2)	2,639 (17.9)	293 (25.2)	13 (19.4)
≥75	2,274 (14.2)	2,090 (14.2)	169 (14.5)	15 (22.4)
BCa laterality				
Right	5,839 (36.5)	5,392 (36.5)	419 (36.1)	28 (41.8)
Left	6,490 (40.6)	5,980 (40.5)	484 (41.6)	26 (38.8)
Bilateral	57 (0.4)	0 (0.0)	56 (4.8)	1 (1.5)
Unknown/missing	3,595 (22.5)	3,380 (22.9)	203 (17.5)	12 (17.9)
Time to diagnosis (median [P25–P75]), years	–	–	4.0 (1.2–7.3) FPC to SPC	3.6 (1.0–6.4) FPC to SPC 0.6 (0.2–1.9) SPC to TPC

May not add to 15,981 due to missing data. BCa, breast cancer; FPC, first primary cancer; P25, percentile 25; P75, percentile 75; SPC, second primary cancer; TPC, third primary cancer.

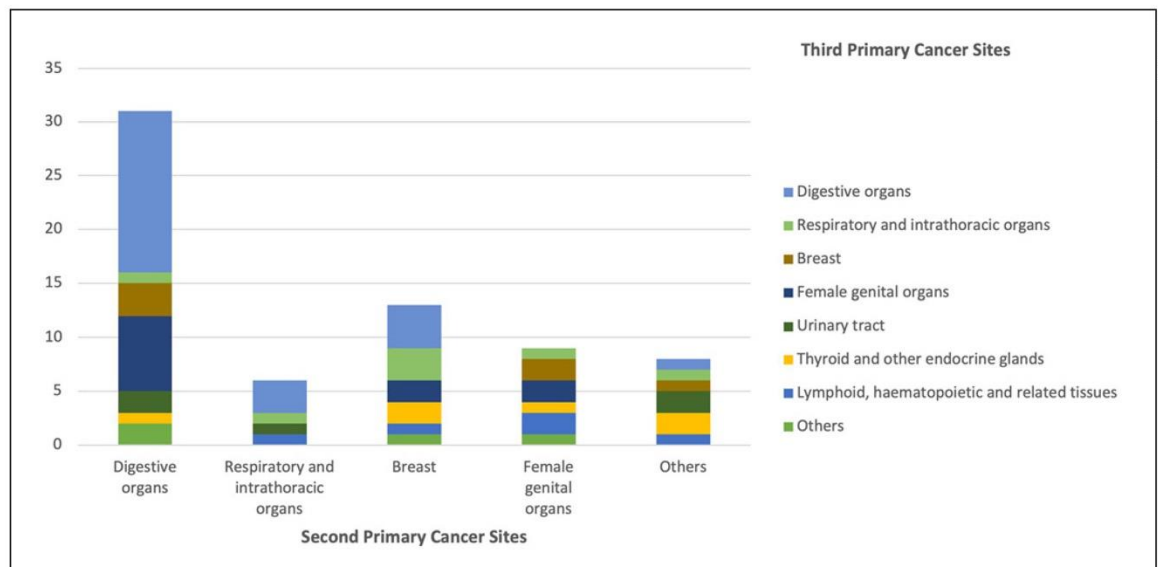


Fig. 1. Distribution of TPCs^a among SPCs^b in female breast FPC patients. FPC, first primary cancer; ICD-10, International Statistical Classification of Diseases and Related Health Problems 10th Revision; SPC, second primary cancer; TPC, third primary cancer. ^a Digestive organs (C15–C26); respiratory and intrathoracic organs (C30–C39); breast (C50); female genital organs (C51–C58); urinary tract (C64–C68); thyroid and other endocrine glands (C73–C75); lymphoid, hematopoietic, and related tissues (C81–C96); and others: lip, oral cavity and pharynx (C1–C14), skin mel-

anoma (C43), mesothelial and soft tissue (C45–C49), ill-defined, secondary, or unspecified sites (C76–C80) defined according to the ICD-10 [13]. ^b Digestive organs (C15–C26), respiratory and intrathoracic organs (C30–C39), breast (C50), female genital organs (C51–C58), others: skin melanoma (C43), urinary tract (C64–C68), eye (C69), brain and other parts of the central nervous system (C70–C72), lymphoid, hematopoietic, and related tissue (C81–C96), uncertain or unknown behavior (D37–D48) defined according to the ICD-10 [13].

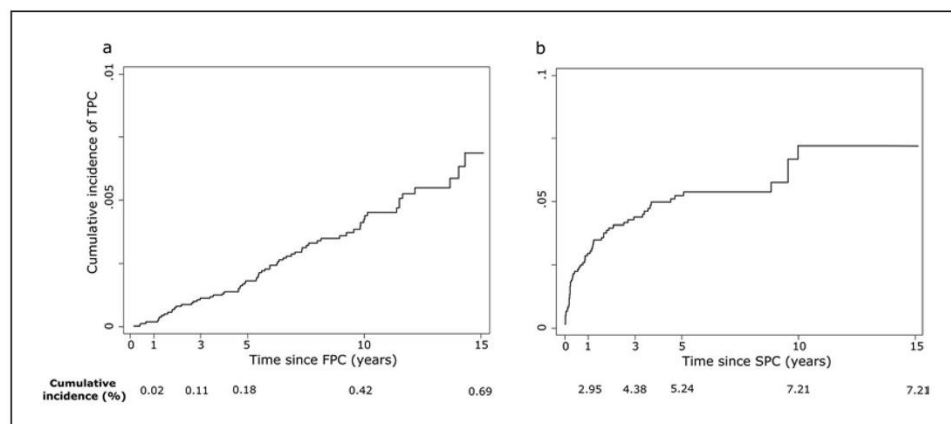


Fig. 2. Cumulative incidence of TPCs, among female breast FPCs (a) and SPCs (b) following a breast FPC, considering the competing event of death. FPC, first primary cancer; SPC, second primary cancer; TPC, third primary cancer. Note that a different scale is used for the two graphs.

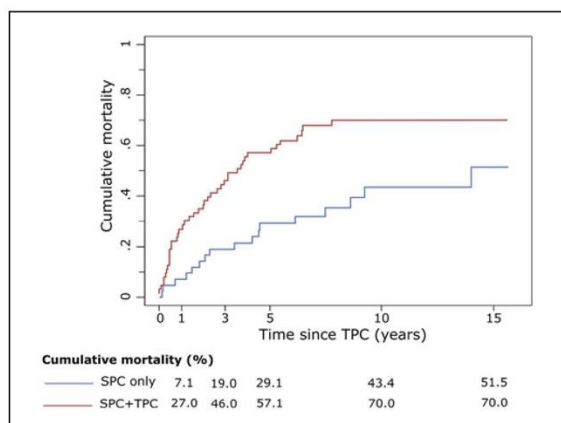


Fig. 3. Observed cumulative all-cause mortality^a of female breast FPCs with an SPC, and with and without a TPC. FPC, first primary cancer; SPC, second primary cancer; TPC, third primary cancer. ^a Calculated using 1 – Kaplan-Meier [16].

Discussion/Conclusion

Overall, the most common TPCs occurred in the digestive system, as well as breast and female genital organs, with a relatively low 15-year cumulative incidence (0.69%) among all breast FPC patients. SPC + TPC patients had a higher probability of all-cause mortality over 15 years compared to patients with an SPC only, highlighting the contribution of a TPC to the mortality of these patients.

Few studies have been conducted on the frequency of MPCs with no population-based studies focusing on the risk and survival of TPCs among BCa survivors, regardless of the SPC site [10]. Generally, the proportion of TPCs is small, ranging from 0.0% to 2.0% of all cancer diagnoses [17]. In Italy, among cancers (all sites) diagnosed between 1976 and 2010, and followed to the end of 2012, 0.3% of patients were diagnosed with a TPC [18]. A previous study conducted in the Netherlands found nearly 7% nonbreast TPCs occurring among 8,752 women diagnosed with bilateral BCa between 1989 and 2008, with a median time of 2.4 years between the first and the second BCa [10]. We estimated a proportion of 0.4% TPCs among breast FPCs, which falls within the previously reported range of TPCs [17].

In the current study, we found that TPCs were more often diagnosed in the digestive system, breast, and female genital organs. This may be because the factors, including host characteristics and environmental exposures, that contribute to the occurrence of FPCs also increase the risk of developing a subsequent primary cancer [6]. Previous studies have shown that caloric excess, obesity, physical inactivity, and reproductive factors may contribute to a clustering of hormone-dependent tumors, including breast, uterine, ovary, and colon tumors [5, 6, 19, 20]. Different hormone receptor statuses are associated with second female genital cancers among BCa survivors, with an increased risk being observed among hormone receptor-negative BCa survivors [21, 22]. Moreover, although cancer hereditary syndromes likely account for only a small proportion of MPCs [6], previous studies have shown that BCa survivors with inherited mutations of BRCA1/2, PTEN, or PT53 have an increased risk of developing several subsequent cancers,

including cancers of the pancreas, contralateral breast, female genital organs, thyroid, and connective tissues [7, 23–25].

The survival of BCa patients who develop a TPC has been seldom described. However, previous studies have found a worse long-term mortality for women with two cancers compared to those with a BCa only [8, 10]. Similarly, the estimates provided here highlight that BCa patients diagnosed with a TPC have a higher mortality. Consequently, the occurrence of MPCs should be considered by clinicians when establishing a prognosis and treatment plan for these patients.

This study is based on data obtained from RORENO, which is representative of BCa survivors from Northern Portugal; however, extrapolating these results to all Portuguese BCa survivors should be done cautiously since there is an uneven distribution of BCa incidence and mortality within the country [26, 27]. Nevertheless, the sample is population-based, and the results may be generalized to settings where the overall patterns of cancer incidence and mortality, and access to health care are not markedly different. Furthermore, an evaluation considering specific SPC or TPC combinations was not possible due to the small number of TPCs observed, and as such, only a descriptive analysis is provided. The current study is also limited by the information available in the registry; thus, we were unable to account for factors such as family history and mutation status, which have been shown to be associated with MPCs [7, 23–25]. Nevertheless, the results of the current study are useful and exhaustive since the incidence and survival of TPCs among female breast FPCs have not been widely reported in previous population-based studies.

The cumulative incidence of TPCs among all breast FPC patients was relatively low with an estimate of 0.69% over a maximum 15-year follow-up period, which were more often observed in the breast, digestive, and female genital organs. Further, breast FPC patients who develop a TPC have a clearly worse survival compared to those with an FPC and SPC only. Considering the increasing number of patients with BCa at risk of developing MPCs, this study highlights the need for additional research to further quantify the burden and survival of TPCs among these patients. This is necessary to adequately determine a comprehensive and personalized treatment approach that considers previous treatments and associated toxicities, and in some cases, may require a more aggressive approach, as well as define surveillance strategies and manage patients' expectations regarding the cancer survivorship burden. Taken together, these may potentially lead to improvements in survival and quality of life among patients with multiple cancers.

Statement of Ethics

The study was approved by the Ethics Committee of the Portuguese Institute of Oncology of Porto (Ref. CES IPO: 332/020), and the analyses were performed according to RORENO guidelines for pseudo anonymization of information used. All procedures performed were in accordance with the ethical standards of the Institutional and/or National Research Committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was granted as exemption from requiring written informed consent by the Ethics Committee of the Portuguese Institute of Oncology of Porto (Ref. CES IPO: 332/020).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

S.M. was responsible for formal analysis, investigation, methodology, and writing – original draft. S.M. and N.L. conceptualized and visualized the study. N.L. supervised the study. All the authors were responsible for data curation and writing – review and editing.

Data Availability Statement

The data that support the findings of this study are available from RORENO, but restrictions apply to the availability of these data, which were used under license for the current study and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of RORENO.

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Second primary cancers among females with a first primary cervical, endometrial and ovarian cancer: a population-based study in North Portugal

Second primary cancers among females with a first primary cervical, endometrial and ovarian cancer: a population-based study in North Portugal

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What does this study add to the clinical work?

This population-based cohort study found that females with gynecological cancer have a higher incidence of second cancers with colon, breast, lung, and pelvic organs being the most common sites of occurrence. Clinicians should adequately manage the expectations and surveillance of survivors of gynecological cancers, valuing symptomatology and physical exploration.

Abstract

Purpose: To estimate the incidence rates of second primary cancers (SPCs) [diagnosed >2 months after a first primary cancer (FPC)], and cumulative incidence and mortality of metachronous SPCs in patients with a cervical, endometrial, or ovarian FPC, and to compare the incidence of SPCs with that expected in the general female population.

Methods: A cohort of patients with cervical, endometrial, or ovarian FPC from the North Region Cancer Registry of Portugal, diagnosed in 2000-2010 (n=5846) was followed until 31/12/2015 for synchronous and metachronous SPCs. Cumulative incidence of metachronous SPCs considering death as a competing event, and incidence rates and standardized incidence ratios (SIR) of SPCs were estimated.

Results: SPCs occurred in 541 (9.3%) patients at a median age of 60 years. SPCs were more frequent among patients with endometrial cancers. Colon, breast, and corpus uteri were the most common sites for an SPC among patients with a gynecological FPC. A higher incidence of all and individual SPCs compared to the general female population was found (SIR=1.96, 95%CI:1.79-2.12) with the most relevant sites being cancers of the colon (SIR=2.32, 95%CI:1.82-2.89), lung (SIR=2.70, 95%CI:1.88, 3.66), cervix (SIR=4.87, 95%CI:3.43, 6.56), endometrium (SIR=5.37, 95%CI:4.16, 6.73) and ovary (SIR=6.06, 95%CI:4.12-8.37). The 10-year cumulative incidence of a metachronous SPC and death for patients with a gynecological FPC was 7.4% and 39.2%, respectively.

Conclusions: In Portugal, patients with a gynecological FPC have a higher incidence of SPCs compared to the general female population, particularly elderly females. Increased surveillance and counselling among these patients are needed.

Keywords: Cervical neoplasms, Endometrial neoplasms, Epidemiology, Population register, Ovary neoplasms, Second primary neoplasm

Introduction

Gynecological tumors including the cervix, uterus and ovary represent nearly 15% of the cancer burden among females worldwide [1, 2]. Cervical cancer is the most common tumor among females in developing countries [1] and accounts for 8% of cancer deaths [1]; endometrial cancer is the sixth most common with an increasing incidence in developed countries [1]; finally, ovarian cancer accounts for 2.5% of female malignancies and 5% of cancer deaths [1, 3]. In Portugal, these cancers represent 14% of cancers diagnosed and 9.5% of cancer deaths, among females [2, 4].

Despite heterogeneity between gynecological cancers, regarding tissue of origin, risk factors, cancer pathological grade and standard treatment [5], survival of gynecological cancers is improving (five-year relative survival for patients diagnosed between 1999 and 2007 is 38%, 62%, and 76% for ovarian, cervical, and endometrial cancers, respectively) [6], due to early diagnosis, cervical cancer screening implementation, and improved treatments and surveillance [7-10]. Previous studies found that survivors of cervical, endometrial, and ovarian cancers have a higher incidence of second primary cancers (SPCs) compared to the general population with standardized incidence ratios (SIRs) of 1.32 (10, 17), 1.74 (18) and 1.04 (19), respectively. Shared genetic, environmental, hormonal or lifestyle risk factors, and side effects of the first primary cancer (FPC) treatment contribute to the occurrence of SPCs [9-15].

This study aimed to estimate the incidence rates of SPCs and the corresponding cumulative incidence of metachronous SPCs after an FPC of the cervix, endometrium, or ovary, diagnosed between 2000 and 2010, in the North of Portugal.

Methods

Study setting

Cancer data was obtained from the North Region Cancer Registry (RORENO), a population-based cancer registry created in 1988. This registry covers the Northern region of Portugal covering nearly one-third of the Portuguese population [16]. RORENO follows the International Agency for Research on Cancer (IARC) rules [17]. Registries maintain quality through regular screening with pre-defined algorithms for validity and consistency [17].

Tumour classification and definition of multiple primary cancers

Tumour topography and morphology were classified according to the International Classification of Diseases for Oncology, Third Edition [18], and then recoded to the International Statistical Classification of Diseases and Related Health Problems, 10th Revision [19]. The definition of SPCs followed the guidelines proposed by the International Association of Cancer Registries and the IARC [20].

Study design

All primary invasive tumours of the cervix uteri (cervical cancer, C53), corpus uteri (endometrial cancer, C54) or ovary (ovarian cancer, C56) diagnosed in adult female residents in Northern Portugal between 1 January 2000 and 31 December 2010 were identified (n=6651). Patients who had a diagnosis of a primary cancer, except skin non melanoma, previous to a cervical, endometrial, or ovarian cancer (n=741), and those who could not be linked to the National Health Service for assessment of vital status (n=64) were excluded. The latter were not significantly different from included participants regarding FPC site (included – 40.5%, 39.3% and 20.2% vs. excluded – 35.9%, 39.1% and 25.0% FPC of the cervix,

corpus, and ovary, respectively; $p=0.592$) or age at diagnosis of FPC [median (percentile 25 – percentile 75; P25-P75): included – 60 (48-71) vs. excluded – 59 (49-74); $p=0.778$].

The remaining patients ($n=5846$) were followed to 31 December 2015 until the diagnosis of an SPC or death, whichever occurred first. The occurrence of a subsequent cancer was ascertained by means of linkage with the list of cases registered by RORENO. Patients known to have died but with an unknown date of death ($n=10$), were imputed a follow-up time equal to the median follow-up of the corresponding five-year age group (from 15–19 to 70–74, and ≥ 75 years) and year of diagnosis.

When more than two primary cancers were observed in the same patient, only the SPC was considered; third and subsequent primaries were disregarded in the present analysis. Due to the thorough evaluation of cancer patients during the initial medical work-up [21], SPCs were classified as synchronous when diagnosed within two months of the FPC or metachronous otherwise [22-24].

Statistical analysis

Patient characteristics were presented as counts and proportions for categorical variables, and median (P25-P75) for continuous variables. To compare quantitative and categorical variables across groups, the Mann-Whitney test and Chi-square test were used, respectively. These analyses were carried out separately for synchronous and metachronous SPCs.

Person-years at risk (PYAR) were calculated as the time from cervical, endometrial, or ovarian FPC diagnosis to SPC diagnosis, death, or end of follow-up, whichever occurred first. The incidence rate of SPCs was estimated for different follow-up periods, by dividing the number of incident SPCs by the PYAR within each time interval.

The incidence of SPCs was compared with age- and calendar year-specific rates in the general female population from Northern Portugal, by calculating SIRs. The observed number of SPCs was divided by

the expected number of cases in the same time period. The latter were estimated by multiplying the incidence of cancer in the general population by the PYAR in the corresponding stratum defined according to five-year age groups (from 15-19 to 70-74, and ≥ 75 years) and calendar year (2000-2015). The incidence of cancer (overall, and for specific cancers: colon, rectum, lung, breast, vagina, cervix, corpus, and ovary) among the general population was acquired from RORENO [16]. The 95% confidence intervals (CIs) of the SIRs were estimated assuming a Poisson probability distribution. SIRs and the corresponding 95%CIs were estimated for all SPCs, and separately for synchronous and metachronous SPCs.

Cumulative incidence of SPCs and corresponding 95%CIs, stratified by FPC site (cervix, corpus, and ovary) and age groups were estimated, considering death as a competing event according to the method by Kalbfleisch and Prentice [25]. We provide plots for SPCs and mortality.

Additionally, several sensitivity analyses were performed defining SPCs as diagnosed six months and one year after the cervical, endometrial, or ovarian FPC.

Statistical analyses were conducted using STATA®15.1 (StataCorp, College Station, TX, USA). Statistical significance was considered when $p < 0.05$. All reported p-values are two-sided.

Results

From 5846 females with a gynecological FPC diagnosed between 2000 and 2010, 541 (9.3%) developed an SPC, with 144 (26.6%) being synchronous (**Table 1**). The median age at diagnosis of an FPC was 60 years. Patients with a metachronous SPC were older compared with those who did not develop an SPC (63 vs. 60 years, $p\text{-value}<0.001$). SPCs were more often diagnosed among females with an endometrial FPC. Median follow-up for all patients was just over 10 years, and the median time between an FPC and a metachronous SPC was 3.8 years.

Incidence rate of second primary cancers and standardized incidence ratios

A 10-fold higher incidence rate of SPCs was identified in the first two months (**Figure 1**) than in the remaining follow-up period. Colon, breast, and endometrium were the most common sites for an SPC among patients with an FPC (**Figure 2**); lung, breast, and endometrium were the most common for cervical FPC; colon, breast, and ovary for endometrial FPC; and colon, breast, and endometrium for ovarian FPC. Cervical SPCs were frequent among females with a cervical, endometrial, or ovarian FPC.

SIRs for all, synchronous and metachronous SPCs are summarized in **Figure 3**. Overall, patients with an FPC had a higher incidence of all types of cancer compared to the general female population (SIR for all FPC=1.96, 95%CI: 1.79-2.12; SIR for cervical FPC=1.92, 95%CI: 1.66-2.19; SIR for endometrial FPC=1.78, 95%CI: 1.56-2.01; SIR for ovarian FPC=2.62, 95%CI: 2.62-3.14). Higher SIRs were observed for colon (SIR=2.32; 95%CI: 1.82-2.89), rectum (SIR=1.75; 95%CI: 1.12-2.52), lung (SIR=2.70; 95%CI: 1.88-3.66), vagina (SIR=37.24; 95%CI: 23.86-53.55), cervix uteri (SIR=4.87; 95%CI: 3.43-6.56), corpus uteri (SIR=5.37; 95%CI: 4.16-6.73) and ovary (SIR=6.06; 95%CI: 4.12-8.37) SPCs. The SPC sites with a higher incidence among survivors of a cervical, endometrial, and ovarian FPC compared to the general population were rectum, lung, vagina, cervix, endometrium, and vagina; colon, vagina, cervix, and

ovary; colon, lung, and corpus uteri, respectively. SIR estimates for metachronous SPCs did not markedly differ from estimates for all SPCs of the same FPC and SPC type.

Cumulative incidence of metachronous second primary cancers and mortality

The five- and 10-year cumulative incidence for metachronous SPCs was 4.3% (95%CI: 3.8-4.8) and 7.4% (95%CI: 6.6-8.1), respectively (**Figure 4**). The corresponding cumulative mortality was 30.9% (95%CI: 29.7-31.2) and 39.2% (95%CI: 37.8-40.5). The 10-year cumulative incidence of SPCs was 6.7% (95%CI: 5.6-7.8) for cervical FPCs, 8.3% (95%CI: 7.1-9.6) for endometrial FPCs and 6.9% (95%CI: 5.3-8.5) for ovarian FPCs. The corresponding cumulative mortality was 35.5% (95%CI: 33.5-37.6), 37.1% (95%CI: 34.8-39.3) and 51.8 (95%CI: 48.7-54.9). The cumulative incidence of SPCs was generally higher among older females (**Supplementary Table 2**).

Sensitivity analyses

Analyses for synchronous SPCs occurring within two, six and 12 months of a gynecological FPC resulted in SIRs of 5.93 (95%CI: 5.00-6.94), 5.30 (95%CI: 4.57-6.09) and 4.17 (95%CI: 3.62-4.75), respectively (**Supplementary Table 3**). Colon, vagina, cervix uteri, corpus uteri, and ovary had a higher incidence compared to the general female population regardless of the time cut-off used to define SPCs. For metachronous SPCs, SIRs were 1.58 (95%CI: 1.43-1.74) for two months, 1.47 (95%CI: 1.32-1.63) for six months and 1.46 (95%CI: 1.31-1.62) for 12 months (**Supplementary Table 4**). The most common sites for an SPC, regardless of the time cut-off, were colon, rectum, lung, and vagina. The 10-year cumulative incidence was 7.4%, 7.2% and 7.4% when defining metachronous SPCs as two, six and 12 months, respectively.

Discussion

Patients with a cervical, endometrial, or ovarian FPC had a higher incidence of SPCs compared with the general female population from Northern Portugal. SPCs occurred more often among patients with an endometrial FPC. The most common sites for an SPC were colon, breast, and endometrium among patients with an FPC. The 10-year cumulative incidence of SPC for patients with an FPC was 7.4% and the corresponding cumulative mortality was 39.2%.

The diagnosis of an SPC among patients with a previous gynecological cancer implies an increased burden for females and requires that health systems turn their focus to a comprehensive surveillance of patients with gynecological cancers [10]. Although previous population-based studies have been published on this topic [8, 10, 11, 13, 26-28], this is the first analyzing the incidence and risk of SPCs among patients with a previous gynecological cancer in Portugal.

A previous study, using the Surveillance, Epidemiology, and End Results (SEER) registry in the USA, reported a higher incidence of SPCs among survivors of gynecological cancer compared to the general female population [10], with a 1.16 SIR for metachronous subsequent primary cancers (>6 months after a previous cancer) [10]. They also found that the most common sites of a subsequent primary cancer were vulva, vagina, leukemia, colon, and rectum [10], which is in line with our results.

SPCs among patients with a cervical FPC

A higher incidence of metachronous SPCs among patients with a cervical FPC has been described in the literature [9, 13, 28, 29]. From the Netherlands, a study with over 12000 patients with a cervical FPC diagnosed in 1989 to 2008 estimated a 1.8 SIR for metachronous (>6 months after the FPC) SPCs [28]. Further, they found that lung, breast, and cancers in the field of radiation, such colon and rectum, corpus uteri, vagina, and bone, were the most frequent sites for SPCs [28]. In Taiwan, a 1.56 SIR for

metachronous SPCs (>12 months after an FPC) was estimated among 35000 patients with a cervical FPC diagnosed in 1997 to 2011 [9]. They observed that esophagus, stomach, colon, rectum, anus, lung, and bone were the most frequent SPC sites [9]. Finally, a 1.08 SIR for metachronous (>6 months after an FPC) SPCs was reported in a Korean cohort study of nearly 73000 patients with a cervical FPC diagnosed in 1993 to 2010; vagina, bone, vulva, anus, bladder, lung and bronchus, uterus, and esophagus were common SPCs [13]. Cervical SPCs were relatively frequent among females with a cervical FPC with eight synchronous and five metachronous SPCs. The main histological types were adenocarcinoma following a squamous cell carcinoma or a basal cell FPC, and squamous cell carcinoma following other specific types of carcinomas or adenocarcinoma. A previous study, by Boakye et al., also observed cervical SPCs following gynecological FPCs [10].

Digestive, genital, and pulmonary organs are described in the literature as frequent SPCs following a cervical cancer [9, 10, 13, 28, 29]. Cervical cancer is mainly associated with human papillomavirus and is also a tobacco smoking associated cancer [30], which are also involved in the etiology of other cancers, such as oropharynx and lung [31, 32]. As such, it is possible that these cancers will occur within the same patient. Moreover, radiotherapy has been suggested as a potential cause for cancers in irradiated areas, such as vagina, colon, and rectum. However, these findings are still debated [29, 32].

SPCs among patients with an endometrial FPC

Previous cohorts have studied the occurrence of subsequent primary cancers following an endometrial cancer [11, 15, 26, 27]. An analysis from the National Cancer Institute's SEER followed 70000 with an endometrial FPC diagnosed in 1973 to 2005 and estimated a 1.04 SIR for metachronous (>23 months after the FPC) SPCs [15]. They found that the most common SPC sites were colon, rectum, bladder, vagina, and soft tissue, which differed depending on the treatment received [15]. In Taiwan, Lee et al followed nearly 12000 patients with an endometrial FPC diagnosed in 1979 to 2008 and estimated a

1.71 SIR for metachronous (>1 month after the FPC) SPCs [27]. They reported vagina, vulva, small intestine, ovary, bladder, kidney, colorectal, lung and breast as the most common metachronous SPCs [27]. These findings are in line with ours, particularly for SPCs in the colon and rectum. We found that endometrial SPCs were common among patients with an endometrial FPC with eight synchronous and three metachronous tumors. The histological types identified were specific types of carcinomas, sarcoma tumors or lymphatic tumors following an adenocarcinoma.

The association between endometrial and colorectal cancer is well known [33], given that obesity and genetic conditions are important risk factors for both [15, 26, 27, 34]. Hereditary nonpolyposis colorectal cancer is an autosomic dominant pathology resulting in high incidence rates of colorectal, endometrial, and ovarian cancers [15, 34]. Radiotherapy is generally used as standard treatment for some stages of endometrial cancer and may be carcinogenic to anatomic organs in the field of exposure, such as genital and rectal cancers [14, 15, 34].

SPCs among patients with an ovarian FPC

Several SIR estimates from studies conducted in Asia are in line with our findings [8, 35]. In Taiwan, Hung et al reported a 2.18 SIR for metachronous (>12 months after the FPC) SPCs among 12000 patients diagnosed with ovarian FPC between 1997 and 2010 [35]. They found colon, rectum, anus, lung, mediastinum, breast, cervix, uterus, bladder, thyroid cancers, and leukemia were frequent SPCs [35]. A study from Korea among nearly 21000 patients with an ovarian FPC followed from 1993 to 2014 estimated a 1.29 SIR for metachronous (>2 months after the FPC) SPCs [8]. They found leukemia, respiratory, colon and rectum, thyroid and breast cancers to be the most common SPCs [8]. From the US, a large study conducted between 1975 and 2016 with 60000 patients with an ovarian FPC estimated a 1.05 SIR for metachronous (>2 months after the FPC) SPCs, and identified myeloid, thyroid digestive and bladder as frequent SPCs [36]. Hormonal influences, diet, and genetic syndromes, such

as Lynch Syndrome, may explain higher incidences for colon, rectum and pelvic SPCs among patients with a previous ovarian cancer compared to the general female population [8, 10, 34-37].

We observed higher cumulative incidence estimates for metachronous SPCs among older patients. A multicentric study by Chatuverdi et al including 100000 patients with a cervical FPC found a higher cumulative incidence of metachronous (>12 months after the FPC) SPC for females under 50 years [29]. For patients with an endometrial FPC, who underwent hysterectomy alone, the cumulative incidence of metachronous (>2 months after the FPC) SPCs, considering death as competing event, was nearly double for females over 50 years old at 3.3% at five-years and 7.2% at 10-years [26].

Strengths and limitations

Our data was obtained from a population-based registry, RORENO, which is highly representative of patients with cancer from Northern Portugal. It has a long-term and complete follow-up with only 1% losses. Further, there is universal, free access to healthcare in Portugal, which contributes for a comprehensive ascertainment of SPCs. However, some limitations should be discussed. Despite the standards accomplished by the registry, namely IARC rules [20] and double validation of all data, misclassification of some synchronous tumors could have occurred due to the contiguity of pelvic organs instead of the classification of a tumor with higher staging, related to medical diagnosis and histological coding improvements [10, 13, 21, 27]. Most literature on this topic excludes synchronous tumors from analysis [8-11, 26]. Although we report estimates for all SPCs, we provide estimates for synchronous and metachronous SPCs considering two, six and 12 months as the cut-off for increased comparability. Furthermore, since we did not have data regarding treatment received, namely, hysterectomy, we could not adequately disentangle SPCs occurring in the cervix and endometrium. The current study lacks information on some clinical data, such as stage at FPC and SPC diagnosis, treatment received by patients, as well as information on patient lifestyle (such as diet and smoking),

family history or known genetic susceptibility. Therefore, we were unable to quantify their contribution, which have been shown by some studies to be associated with higher-than-expected SPCs [9, 10, 34, 35].

Conclusions

This population-based cohort study found that females with gynecological FPCs have a higher incidence of SPCs compared with the observed in the general female population. The most common sites for SPCs were colon, breast, lung, and pelvic organs. These findings may help healthcare clinicians manage the expectations and surveillance of survivors with gynecological cancers, valuing symptomatology and physical exploration.

Statements and Declarations

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Author contributions: E Gonçalves: Study conception and design, Data preparation and collection, Data analysis, Manuscript writing. F Fontes: Study conception and design, Manuscript editing. JR Rodrigues: Study conception and design, Data management, Manuscript editing. R Calisto: Study conception and design, Data management, Manuscript editing. MJ Bento: Study conception and design, Data management, Manuscript editing. N Lunet: Study conception and design, Manuscript editing. S Morais: Study conception and design, Data preparation and collection, Data management, Manuscript editing.

All authors contributed to the study conception and design. Data preparation and collection were performed by Elisabete Gonçalves, Jéssica Rocha Rodrigues, Rita Calisto, Maria José Bento, and

Samantha Morais. Analyses were performed by Elisabete Gonçalves and Samantha Morais. The first draft of the manuscript was written by Elisabete Gonçalves, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data availability: The data that support the findings of this study are available from RORENO, but restrictions apply to the availability of these data, which were used under license for the current study and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of RORENO.

Ethics approval: The study was approved by the Ethics Committee of the Portuguese Institute of Oncology of Porto (Ref. CES IPO: 332/020) and the analyses were performed according to RORENO guidelines ensuring the anonymity of information used.

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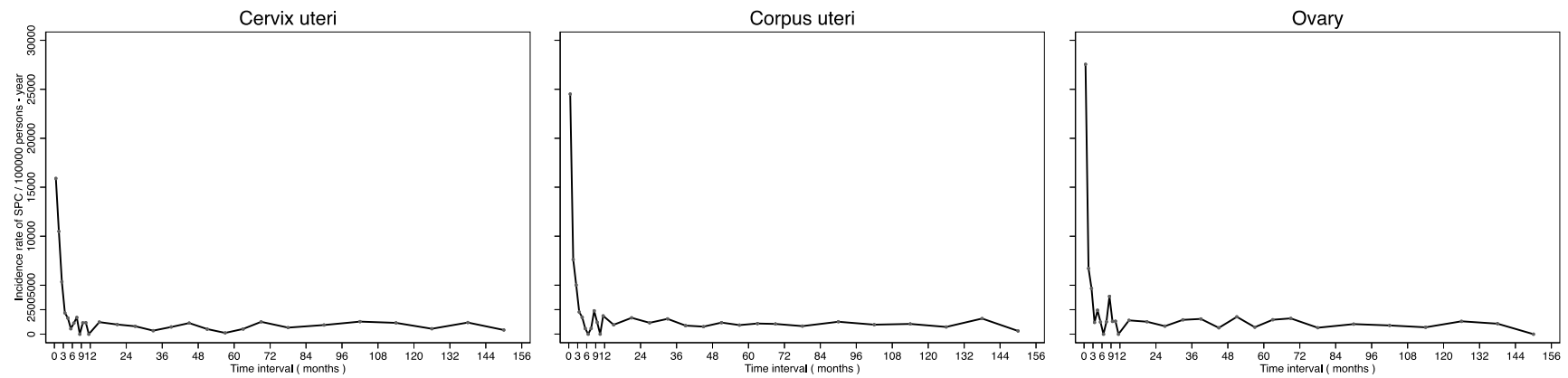


Fig. 1. Incidence rates of second primary cancers since the diagnosis of a cervical, endometrial or ovarian first primary cancer.

FPC, first primary cancer; SPC, second primary cancer.

Incidence rates were estimated for and represented in the respective midpoint of the following intervals: each month in the first year of follow-up, every six months from the second to the sixth year of follow-up, and then for each year of follow-up.

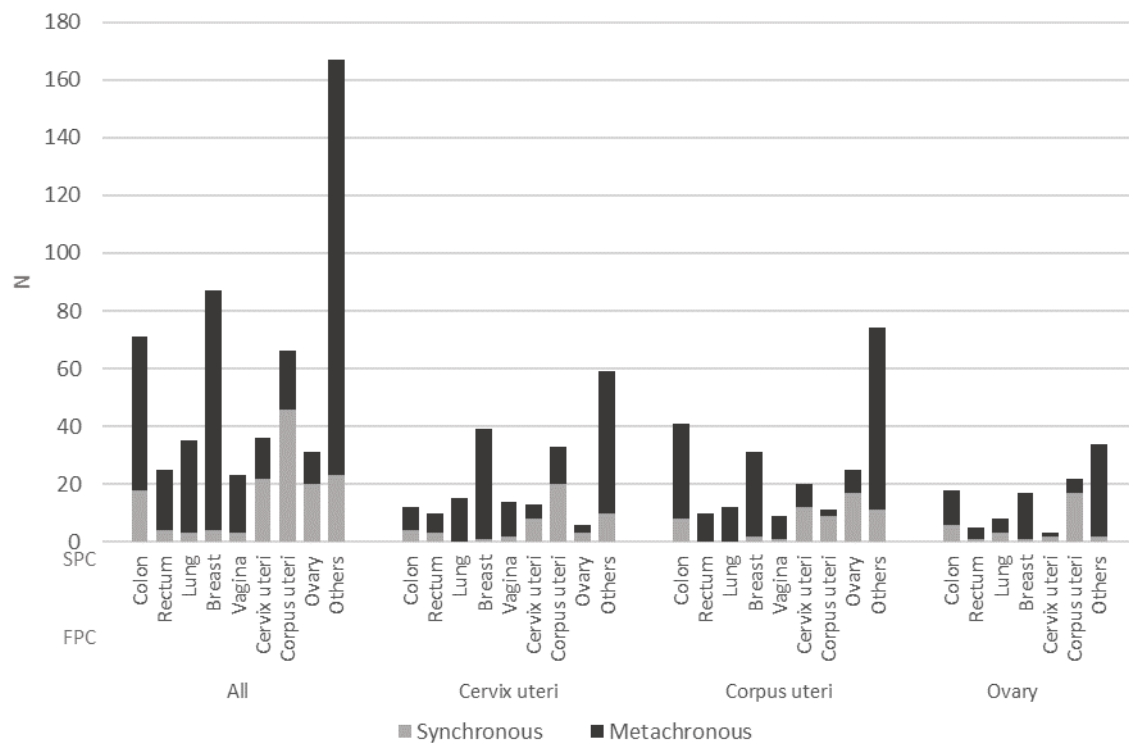


Fig. 2. Distribution of **synchronous** and **metachronous** second primary cancers^a among females with a first primary cancer of the cervix uteri, corpus uteri or ovary.

FPC, first primary cancer; SPC, second primary cancer.

^a Colon (C18), Rectum (C19-20), Lung (including trachea and bronchus; C33-C34), Breast (C50), Vagina (C52), Cervix uteri (C53), Corpus uteri (C54), Ovary (C56). Others include: Lip, oral cavity and pharynx (C00-14), Oesophagus (C15), Stomach, (C16), Small intestine (C17), Liver and intrahepatic bile ducts (C22), Gallbladder, and other and unspecified parts of biliary tract (C23-C24), Pancreas (C25), Skin (C43), Mesothelioma (C45), Kaposi sarcoma (C46), Other connective and soft tissue (C49), Vulva (C51), Uterus, part unspecified (C55), Kidney (C64), Bladder (C67), Brain and Central Nervous System (C70-C72), Thyroid gland (C73), Without specification of site (C80), Hodgkin lymphoma (C81), Non-Hodgkin lymphoma (C85), Multiple myeloma (C90), Lymphoid leukaemia (C91), Myeloid leukaemia (C92-C94), Myelodysplastic syndromes (D46) [18].

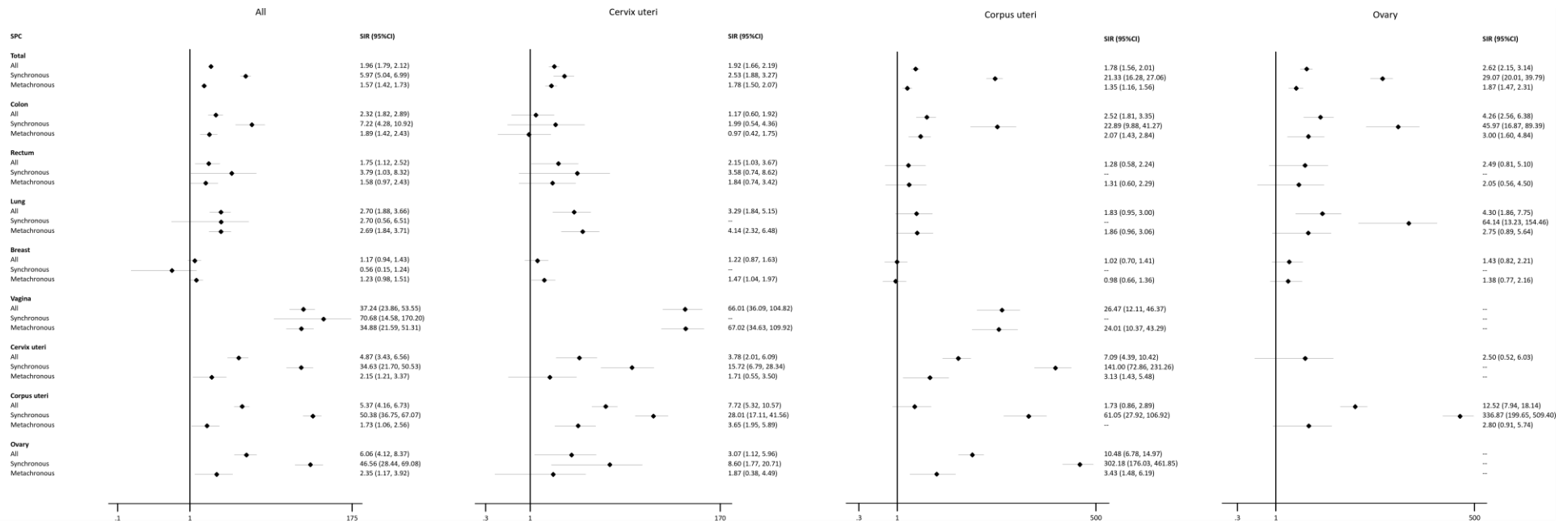


Fig. 3. Standardized incidence ratios and 95% confidence interval of selected second primary cancers^a in patients with a first primary cancer of the cervix uteri, corpus uteri or ovary.

95%CI, 95% confidence interval; FPC, first primary cancer; SIR, standardized incidence ratio; SPC, second primary cancer; --, SIRs were not estimated as less than 3 SPCs were observed.

^a Colon (C18), Rectum (C19-20), Lung (including trachea and bronchus; C33-C34), Breast (C50), Vagina (C52), Cervix uteri (C53), Corpus uteri (C54), Ovary (C56) [18].

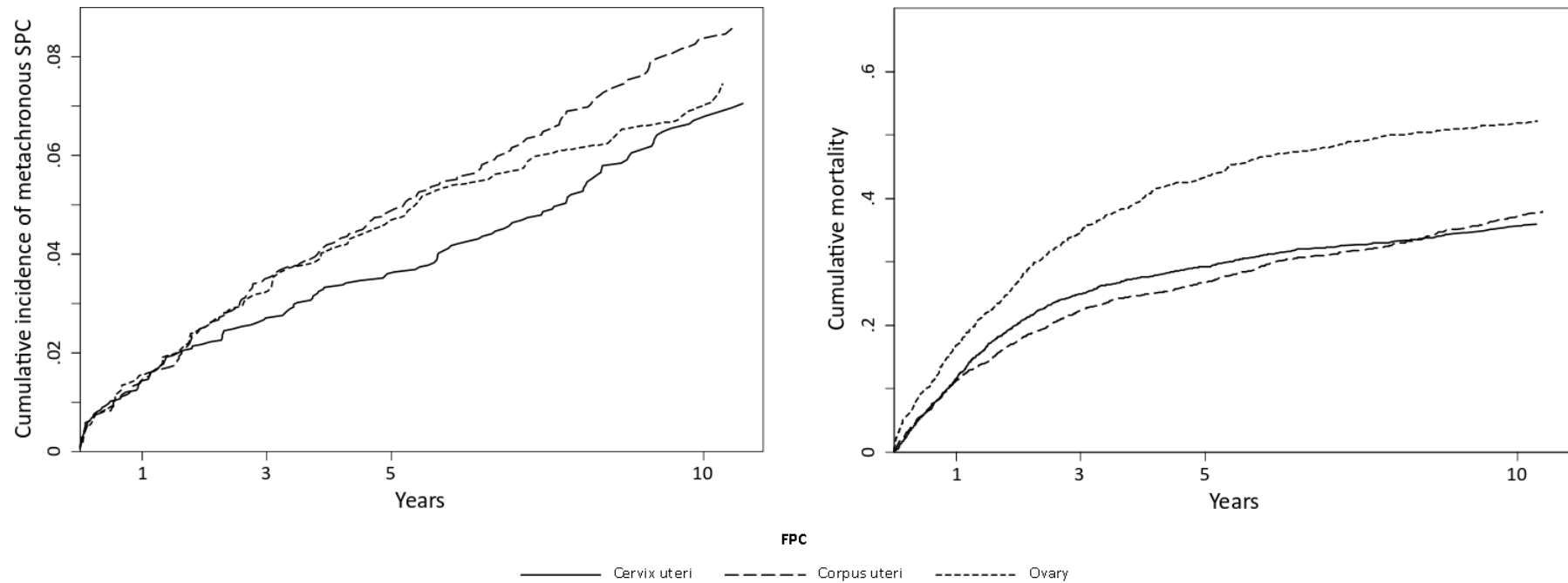


Fig. 4. Cumulative incidence **metachronous** second primary cancers and death, considering the competing event of death, among females with a first primary cancer of the cervix uteri, corpus uteri or ovary.

FPC, first primary cancer; SPC, second primary cancer.

* Note that a different scale is used for the two outcomes.

Table 1. Features of patients with a first primary cancer of the cervix uteri, corpus uteri or ovary with **synchronous** and **metachronous** second primary cancers, and without a second primary cancer.

	Total N=5846 (100.0%)	Patients without an SPC N=5305 (90.7%)		Patients with an SPC N=541 (9.3%)				
			<i>p-value</i> All SPC vs. no SPC	Synchronous (n=144)	<i>p-value</i> Synchronous SPC vs. no SPC	Metachronous (n=397)	<i>p-value</i> Metachronous SPC vs. no SPC ^a	<i>p-value</i> Synchronous SPC vs. Metachronous SPC
Age at diagnosis of FPC, years [median (P25-P75)]	60 (48-71)	60 (48-71)	<0.001	62 (51-72)	0.112	63 (53-72)	<0.001	0.620
<45	1087 (18.6)	1027 (19.4)		16 (11.1)		44 (11.1)		
45-54	1081 (18.5)	974 (18.4)		33 (22.9)		74 (18.6)		
55-64	1363 (23.3)	1240 (23.4)		31 (21.5)		92 (23.2)		
65-74	1380 (23.6)	1225 (23.1)		37 (25.7)		118 (29.7)		
≥75	934 (16.0)	838 (15.78)	<0.001	27 (18.7)	0.126	69 (17.4)	<0.001	0.770
FPC site [N (%)]								
Cervix uteri (C53)	2369 (40.5)	2168 (40.9)		51 (35.4)		150 (37.8)		
Corpus uteri (C54)	2296 (39.3)	2063 (38.9)		60 (41.7)		173 (43.6)		
Ovary (C56)	1181 (20.2)	1074 (20.2)	0.142	33 (22.9)	0.427	74 (18.6)	0.247	0.542
Follow-up, years [median (P25-P75)] ^b	10.2 (7.5-13.0)	10.0 (7.4-12.9)	<0.001	0.1 (0.0-0.1)	<0.001	3.8 (1.4-7.4)	<0.001	<0.001
Dead [N (%)]^c	2665 (45.6)	2354 (44.4)	<0.001	90 (62.5)	<0.001	221 (55.5)	<0.001	0.124

FPC, first primary cancer; P25, percentile 25; P75, percentile 75; SPC, second primary cancer.

May not add to 5846 due to missing data.

^a Patients without an SPC are those who survived more than two months after diagnosis of the FPC.

^b Follow-up to 31 December 2015 until SPC, death or end of follow-up. Median follow-up time was estimated using the reverse Kaplan-Meier [25].

^c Follow-up to 31 December 2015.

Supplementary Table 1. Number of expected and observed selected second primary cancers^a in patients with a first primary cancer of the cervix uteri, corpus uteri or ovary.

SPC site	All FPC		Cervix uteri FPC		Corpus uteri FPC		Ovary FPC	
	Exp N	Obs N	Exp N	Obs N	Exp N	Obs N	Exp N	Obs N
Total								
All	276.56	541	104.67	201	131.10	233	40.79	107
Synchronous	24.11	144	20.16	51	2.81	60	1.13	33
Metachronous	252.45	397	84.51	150	128.29	173	39.66	74
Colon								
All	31.00	72	10.28	12	16.25	41	4.46	19
Synchronous	2.49	18	2.01	4	0.35	8	0.13	6
Metachronous	28.50	54	8.26	8	15.90	33	4.33	13
Rectum								
All	13.71	24	4.65	10	7.05	9	2.01	5
Synchronous	1.05	4	0.84	3	--	<3	--	<3
Metachronous	12.66	20	3.81	7	6.89	9	1.95	4
Lung								
All	12.98	35	4.56	15	6.56	12	1.86	8
Synchronous	1.11	3	--	<3	--	<3	0.05	3
Metachronous	11.87	32	3.62	15	6.44	12	1.81	5
Breast								
All	74.45	87	32.02	39	31.24	32	11.19	16
Synchronous	7.08	4	--	<3	--	<2	--	<3
Metachronous	67.37	83	25.92	38	30.55	30	10.89	15
Vagina								
All	0.64	24	0.21	14	0.34	9	--	<3
Synchronous	0.04	3	--	<3	--	<3	--	<3
Metachronous	0.60	21	0.18	12	0.33	8	--	<3
Cervix uteri								
All	7.60	37	3.44	13	2.96	21	1.20	3
Synchronous	0.63	22	0.51	8	0.08	12	--	<3
Metachronous	6.97	15	2.93	5	2.88	9	--	<3
Corpus uteri								
All	12.48	67	4.27	33	6.37	11	1.84	23
Synchronous	0.91	47	0.71	20	0.15	9	0.05	18
Metachronous	11.57	20	3.56	13	--	<3	1.78	5
Ovary								
All	5.12	31	1.96	6	2.38	25	--	<3
Synchronous	0.43	20	0.35	3	0.06	17	--	<3
Metachronous	4.69	11	1.61	3	2.33	8	--	<3

Exp, expected; FPC, first primary cancer; Obs, observed; SPC, second primary cancer; --, expected number of SPCs was not estimated as less than 3 SPCs were observed.

^a Colon (C18), Lung (including trachea and bronchus; C33-C34), Breast (C50), Vagina (C52), Cervix uteri (C53), Corpus uteri (C54), Ovary (C56) [18].

Supplementary Table 2. Cumulative incidence of second primary cancers considering the competing event of death.

	Years	Cumulative Incidence of SPC [% (95%CI)]				Cumulative mortality [% (95%CI)]			
		1	3	5	10	1	3	5	10
All	Total	2.9 (2.5-3.3)	4.6 (4.0-5.1)	5.7 (5.1-6.3)	8.6 (7.9-9.4)	13.8 (12.9-14.7)	27.5 (26.4-28.7)	32.8 (31.6-34.0)	40.6 (39.2-41.0)
	FPC site								
	Cervix uteri (C53)	2.9 (2.2-3.6)	4.2 (3.4-5.0)	5.0 (4.2-5.9)	8.1 (7.0-9.3)	11.9 (10.6-13.2)	26.0 (24.3-27.8)	30.6 (28.7-32.4)	36.6 (34.6-38.7)
	Corpus uteri (C54)	2.9 (2.2-3.6)	5.0 (4.1-5.9)	6.2 (5.2-7.2)	9.5 (8.2-10.8)	11.8 (10.5-13.1)	23.2 (21.5-24.9)	27.9 (26.0-29.7)	37.7 (35.5-39.9)
	Ovary (C56)	3.0 (2.0-4.0)	4.6 (3.4-5.8)	5.8 (4.5-7.2)	8.0 (6.3-9.6)	21.6 (19.2-23.9)	38.9 (36.1-41.7)	46.9 (44.0-49.7)	54.8 (51.9-57.8)
	Age at FPC diagnosis, years								
	<45	1.7 (0.9-2.4)	2.5 (1.6-3.4)	3.3 (2.3-4.4)	5.2 (3.8-6.6)	6.7 (5.3-8.2)	15.1 (12.9-17.2)	17.5 (15.2-19.7)	20.4 (17.9-22.8)
	45-54	3.0 (2.0-4.0)	4.4 (3.2-5.6)	5.3 (4.0-6.)	8.9 (7.1-10.8)	8.6 (6.9-10.3)	18.6 (16.2-20.9)	22.0 (19.5-24.5)	27.3 (24.6-30.1)
	55-64	2.2 (1.4-3.0)	4.0 (3.0-5.0)	4.5 (3.4-5.6)	8.4 (6.7-10.0)	9.9 (8.3-11.5)	21.8 (19.6-24.1)	27.6 (24.2-30.0)	33.8 (31.2-36.4)
	65-74	3.6 (2.6-4.5)	5.6 (4.4-6.8)	7.4 (6.0-8.7)	10.8 (9.1-12.6)	14.1 (12.2-15.9)	31.7 (29.2-34.2)	39.1 (36.6-41.7)	51.9 (49.0-54.8)
	≥75	4.3 (3.0-5.6)	6.6 (5.0-8.2)	8.0 (6.2-9.7)	9.7 (7.8-11.7)	33.4 (30.4-36.4)	54.5 (51.3-57.7)	61.3 (58.2-64.4)	74.6 (71.5-77.7)
	Total	1.5 (1.1-1.8)	3.1 (2.6-3.7)	4.3 (3.8-4.8)	7.4 (6.6-8.1)	12.4 (11.5-13.2)	25.7 (24.6-26.9)	30.9 (29.7-31.2)	39.2 (37.8-40.5)
	FPC site								
	Cervix uteri (C53)	1.4 (0.9-1.9)	2.7 (2.0-3.4)	3.6 (2.8-4.4)	6.7 (5.6-7.8)	11.5 (10.1-12.8)	25.0 (23.2-26.7)	29.2 (27.3-31.0)	35.5 (33.5-37.6)
	Corpus uteri (C54)	1.5 (1.0-2.0)	3.5 (2.7-4.3)	4.9 (4.0-5.8)	8.3 (7.1-9.6)	11.2 (9.9-12.5)	22.3 (20.5-24.0)	26.8 (24.9-28.7)	37.1 (34.8-39.3)
	Ovary (C56)	1.5 (0.8-2.3)	3.2 (2.1-4.2)	4.7 (3.4-6.0)	6.9 (5.3-8.5)	16.7 (14.5-19.0)	34.5 (31.6-37.4)	43.4 (40.4-46.4)	51.8 (48.7-54.9)
Metachronous	Age at FPC diagnosis, years								
	<45	0.8 (0.2-1.3)	1.7 (0.9-2.5)	2.4 (1.4-3.3)	4.2 (2.9-5.5)	6.5 (5.0-8.0)	14.3 (12.2-16.4)	16.7 (14.4-18.9)	19.5 (17.1-22.0)
	45-54	0.9 (0.3-1.4)	2.3 (1.4-3.2)	3.4 (2.3-4.5)	6.9 (5.2-8.7)	8.2 (6.6-9.9)	18.5 (16.2-20.9)	21.5 (18.9-24.0)	26.7 (24.9-29.5)
	55-64	1.2 (0.6-1.7)	2.8 (1.9-3.7)	3.5 (2.5-4.5)	7.3 (5.7-8.9)	9.0 (7.5-10.6)	20.5 (18.3-22.7)	26.0 (23.6-28.4)	32.6 (29.9-35.3)
	65-74	1.9 (1.1-2.5)	3.7 (2.7-4.8)	5.8 (4.5-7.0)	9.5 (7.8-11.3)	13.2 (11.4-15.1)	30.3 (27.8-32.9)	37.9 (35.2-40.5)	51.5 (48.5-54.5)
	≥75	3.1 (1.9-4.3)	5.4 (3.9-7.0)	7.1 (5.3-8.8)	8.9 (6.9-11.0)	29.2 (26.1-32.3)	50.9 (47.4-54.3)	58.5 (55.1-61.9)	73.5 (70.0-76.9)

95%CI, 95% confidence interval; FPC, first primary cancer; SPC, second primary cancer.

Supplementary Table 3. Sensitivity analyses defining **synchronous** second primary cancers as occurring two months, six months and one year after cervix uteri, corpus uteri or ovary first primary cancer.

	Estimates according to the cut-off for defining synchronous SPC		
	2 months	6 months	1 year
Synchronous SPC^a [N (%)]			
All	143 (26.4)	186 (34.4)	211 (39.0)
Colon	18 (12.6)	23 (12.4)	24 (11.4)
Rectum	4 (2.8)	4 (2.2)	7 (3.3)
Lung	3 (2.1)	4 (2.2)	4 (1.9)
Breast	4 (2.8)	9 (4.8)	10 (4.7)
Vagina	3 (2.1)	4 (2.2)	5 (2.4)
Cervix uteri	22 (15.4)	27 (14.5)	29 (13.7)
Corpus uteri	46 (32.2)	56 (30.1)	58 (27.5)
Ovary	20 (14.0)	25 (13.4)	27 (12.8)
Standardized incidence ratios of synchronous SPC^a (95%CI)			
All	5.93 (5.00-6.94)	5.30 (4.57-6.09)	4.17 (3.62-4.75)
Colon	7.22 (4.28-10.92)	6.14 (3.89-8.89)	4.35 (2.79-6.26)
Rectum	3.79 (1.03-8.32)	2.47 (0.67-5.41)	2.89 (1.16-5.40)
Lung	2.70 (0.56-6.51)	2.56 (0.70-5.62)	1.81 (0.49-3.97)
Breast	0.56 (0.15-1.24)	0.90 (0.41-1.58)	0.71 (0.34-1.21)
Vagina	70.68 (14.58-170.2)	59.33 (16.16-130.03)	48.45 (15.73-99.25)
Cervix uteri	34.63 (21.70-50.53)	25.99 (17.13-36.67)	18.16 (12.16-25.34)
Corpus uteri	50.28 (36.81-65.82)	38.90 (29.39-49.74)	26.54 (20.15-33.79)
Ovary	46.56 (28.44-69.08)	38.29 (24.78-54.69)	27.87 (18.37-39.32)

95%CI, 95% confidence interval; SPC, second primary cancer.

^a Colon (C18), Lung (including trachea and bronchus; C33-C34), Breast (C50), Vagina (C52), Cervix uteri (C53), Corpus uteri (C54), Ovary (C56) [18].

Supplementary Table 4. Sensitivity analyses defining **metachronous** second primary cancers as occurring two months, six months and one year after cervix uteri, corpus uteri or ovary first primary cancer.

	Estimates according to the cut-off for defining metachronous SPC		
	2 months	6 months	1 year
Metachronous SPC [N (%)]	397 (73.4)	351 (64.9)	326 (60.3)
Cumulative incidence of metachronous SPC [% (95%CI)]			
At 1 year	1.5 (1.1-1.8)	1.0 (0.7-1.3)	1.2 (0.9-1.5)
At 3 years	3.1 (2.6-3.7)	2.7 (2.3-3.1)	2.7 (2.3-3.2)
At 5 years	4.3 (3.8-4.8)	3.9 (3.4-4.4)	4.1 (3.5-4.7)
At 10 years	7.4 (6.6-8.1)	7.2 (6.4-8.0)	7.4 (6.5-8.2)
Metachronous SPC^a [N (%)]			
Colon	54 (13.6)	48 (13.7)	47 (14.2)
Rectum	20 (5.0)	20 (5.7)	17 (5.2)
Lung	32 (8.1)	31 (8.8)	31 (9.5)
Breast	83 (20.9)	77 (21.9)	76 (23.3)
Vagina	21 (5.3)	20 (5.7)	19 (5.8)
Cervix uteri	15 (3.6)	9 (2.6)	7 (2.1)
Corpus uteri	20 (5.0)	10 (2.8)	8 (2.4)
Ovary	11 (2.8)	6 (1.7)	4 (1.2)
Standardized incidence ratios of metachronous SPC^a (95%CI)			
All	1.58 (1.43-1.74)	1.47 (1.32-1.63)	1.46 (1.31-1.62)
Colon	1.86 (1.39-2.39)	1.76 (1.3-2.29)	1.84 (1.36-2.41)
Rectum	1.66 (1.03-2.44)	1.74 (1.08-2.55)	1.59 (0.94-2.41)
Lung	2.69 (1.84-3.71)	2.71 (1.84-3.75)	2.88 (1.95-3.97)
Breast	1.23 (0.98-1.51)	1.21 (0.96-1.49)	1.16 (0.90-1.45)
Vagina	34.88 (21.59-51.31)	34.66 (21.17-51.42)	35.1 (21.13-52.56)
Cervix uteri	2.01 (1.10-3.19)	1.52 (0.73-2.6)	1.17 (0.47-2.18)
Corpus uteri	1.73 (1.06-2.56)	0.91 (0.43-1.55)	0.78 (0.34-1.40)
Ovary	2.35 (1.17-3.92)	1.34 (0.49-2.61)	0.96 (0.26-2.11)

95% CI, 95% confidence interval; SPC, second primary cancer.

^a Colon (C18), Lung (including trachea and bronchus; C33-C34), Breast (C50), Vagina (C52), Cervix uteri (C53), Corpus uteri (C54), Ovary (C56) [18].

DISCUSSION

For all cancers and for females, who have a higher life expectancy, an increasing cancer incidence is expected by 2040. Furthermore, cancer screening strategies, earlier detection and more effective treatment have resulted in improvements in overall survival. The long-term side effects of chemotherapy and/or radiation therapy, advanced diagnostic sensitivity tools for screening programs and/or follow-up tests, as well as the persisting effects of genetic and behavioral risk factors contribute for an increased risk of a subsequent cancer among survivors of cancer. It has been shown that the risk of other primary cancers is increasing among cancer survivors, however, several factors may influence the number of subsequent primary cancers, such as the definition used, the patient population under study, the follow-up time, and the overall survival of the FPC. Understanding the dynamics of occurrence and survival of SPCs is of particular importance and may help in defining priorities in clinical practice. Furthermore, dealing with patients' expectations regarding the burden of survivorship, as well as economic consequences are also relevant.

In Northern Portugal, we found that over time, survivors of cancer had increasing trends of incident rates of cancer. Specifically, incidence rates and SIRs for SPCs were higher among patients diagnosed with cancer, with distinct patterns observed based on sex and FPC site: a higher proportion of SPCs was diagnosed among males than females and moreover it was particularly evident for FPCs and SPCs of the lip, oral cavity, pharynx, esophagus and larynx among males, and colon and rectum, lung, ovary, and cervix among females.

Breast, endometrial, ovarian, and cervical cancers have a representative burden among females worldwide and in Portugal. Furthermore, these cancers have a relatively high survival, which may result in a high number of SCPs among patients with a previous cancer. Patients with a breast or a gynecological cancer had a higher incidence of cancer compared to the general female population. We also found that patients with a breast FPC and synchronous SPC had a 1.5-fold higher hazard of death, while those with a metachronous SPC had almost a three-fold higher hazard of death when compared to patients with a breast FPC only. TPCs following a breast FPC occurred in 0.4% of FPCs and we found that the age-adjusted hazard ratio for death was almost three times higher compared to matched patients with an SPC only.

We found patients with gynecological cancer had a higher incidence of all and individual SPCs compared to the general female population was found and the most relevant sites were colon, lung, cervix, endometrium, and ovary. The 10-year cumulative incidence of SPC for patients with a gynecological FPC was 7.4% and the 10-year cumulative mortality was 39.2%.

Considering the projections on increasing cancer incidence globally (2) and in Portugal (7), as well as improvements in the long-term survival for patients with cancer (61), the impact of cancer on health status and healthcare utilization access and cost for a properly healthcare system financial sustainability is a remarkable issue (94-97). Higher medical complexity conditions are common throughout survivorship, as well as adverse psychological and cognitive issues, and the risk of recurrence or subsequent cancers (95-97). It is specifically concerning among female survivors of cancer, who are described to have their long-term health impaired, because of physical and psychosocial aspects, causing a high demand for healthcare services (95). Thus, the mode of delivery healthcare provided to survivors of cancer is expected to shift (98).

This thesis provides a description of the increasing trend, as well as the risk and survival of SPCs for specific female cancers and TPCs among females with a previous breast cancer. It represents the first comprehensive analysis in Northern Portugal for breast and gynecological cancers, concerning cancer-survivorship. The burden of SPCs was previously addressed in this setting for frequency and survival (72); the impact of breast cancer, which is the most incident cancer worldwide and in Portugal (2, 8), and of gynecological tumors, which are less studied, have not yet been evaluated. We used robust methodologies to assess the risk and survival associated with SPCs and TPCs among female survivors of cancer. We applied an analytical framework for understanding the dynamics of SPCs within an expanding population of female survivors of cancer and we have a large cohort of FPCs followed for at least 10 years.

Nevertheless, we must consider the general methodological challenges commonly encountered in estimating the survival of patients with MPCs. This thesis also underscores the imperative of comprehensive and timely data collection by cancer registries. In fact, in recent years, the *Registo Oncológico Nacional* has been established, which will allow for future work. Some clinical data, such as stage at FPC or SPC diagnosis, treatment performed, and as well as some information on lifestyle is expected to expand future analyses. Furthermore, this thesis highlights the need for the development of strategies to facilitate the study of the contribution of specific primary cancers to the overall survival of patients with MPCs.

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