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EPIDEMIOLOGY

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 N = 15,981 (100.0%)	Patients without an SPC N = 14,752 (92.3%)		Patients with an SPC N = 1229 (7.7%)				
			p-value All SPC vs. no SPC	**Synchronous** (n = 215)	*p-value* Synchronous SPC vs. no SPC	**Metachronous** (n = 1014)	*p-value* Metachronous SPC vs. no SPC[a]	*p-value* Synchronous SPC vs. Metachronous SPC
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

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

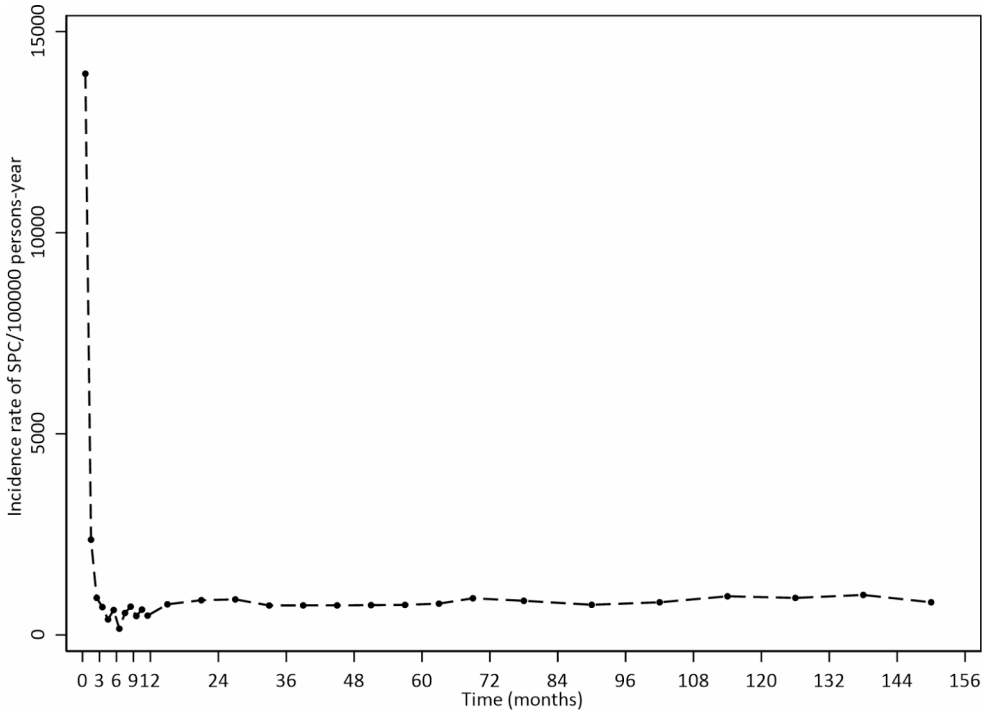

Fig. 1 Incidence rates of second primary cancers since the diagnosis of the first primary breast cancer. FPC, first primary cancer; SPC, second primary cancer. Incidence rates were estimated for and represented in the respective midpoint of the following intervals: each month in the first year of follow-up,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

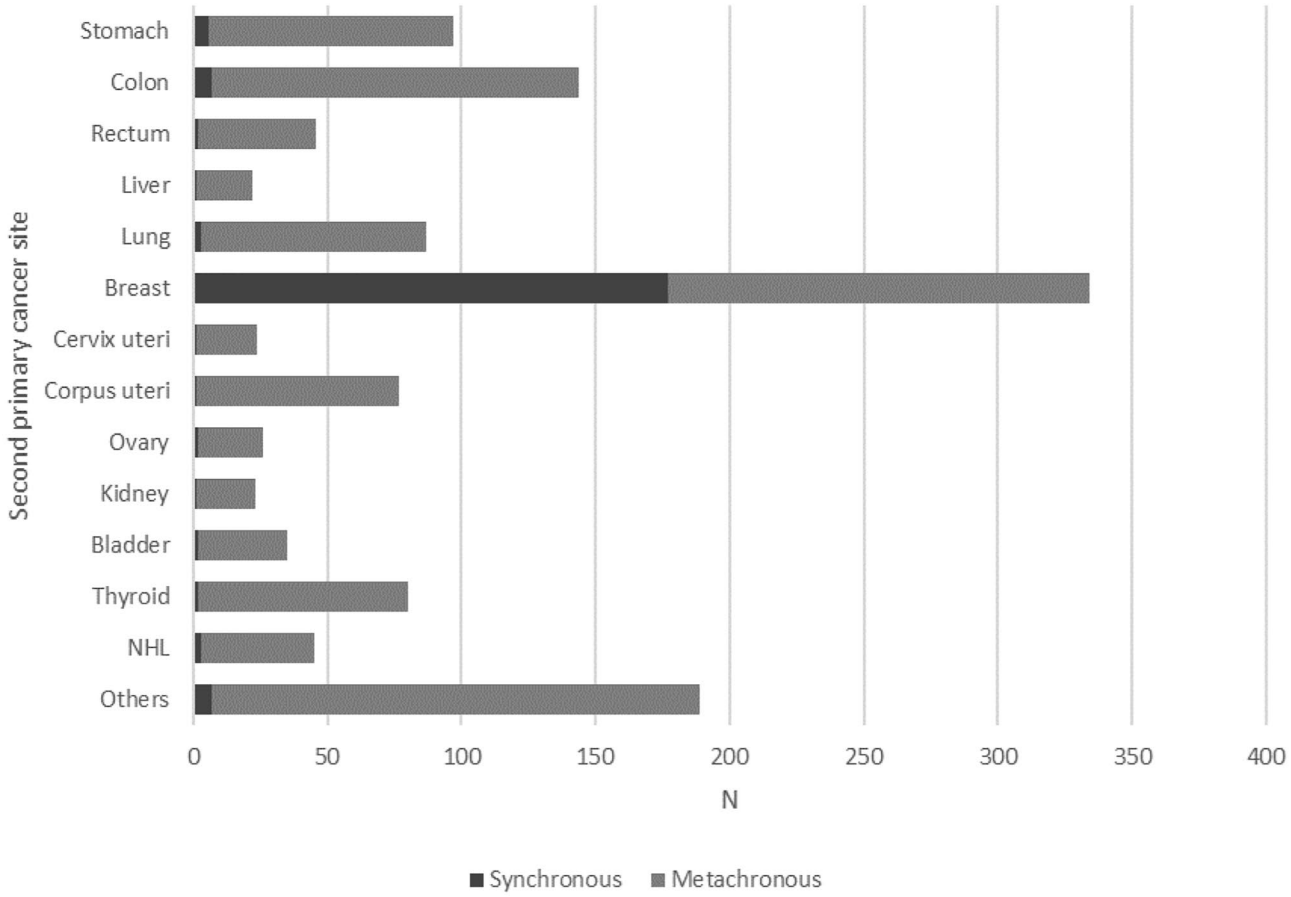

Fig. 2 Distribution of synchronous and metachronous second primary cancers[a] among females with a first primary breast cancer. NHL, non-Hodgkin lymphoma. [a] Stomach (C16), Colon (C18), Rectum (C19-C20), Liver and intrahepatic bile ducts (C22), Lung (including trachea and bronchus; C33-C34), Breast (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 (C40-41), 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 protocoled 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.

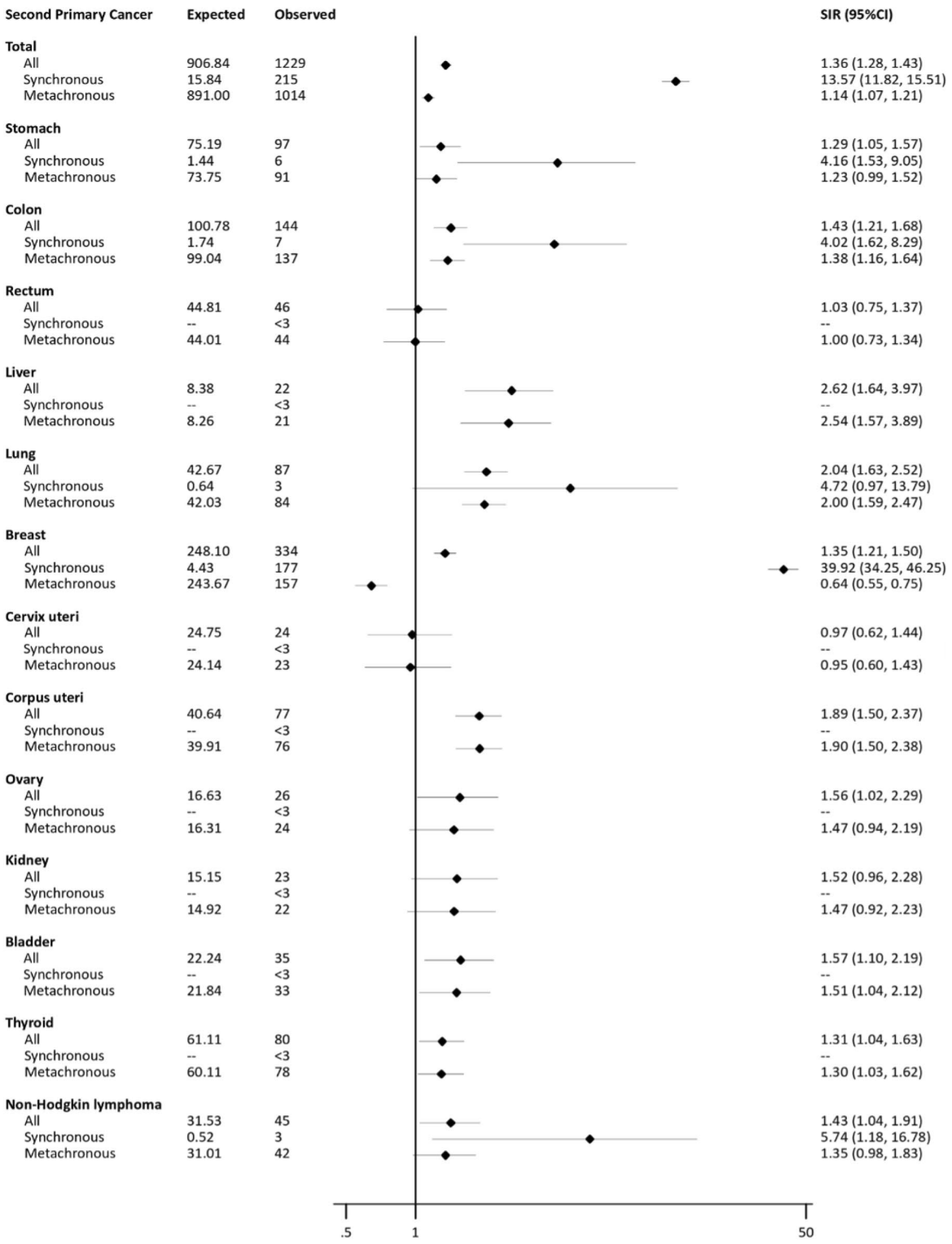

Fig. 3 Standardized incidence ratios and 95% confidence interval of selected second primary cancers[a] in patients with first primary breast cancer. 95%CI, 95% confidence interval; SIR, standardized incidence ratios; --, expected number of SPCs and SIRs (95%CI) were not estimated as less than three SPCs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

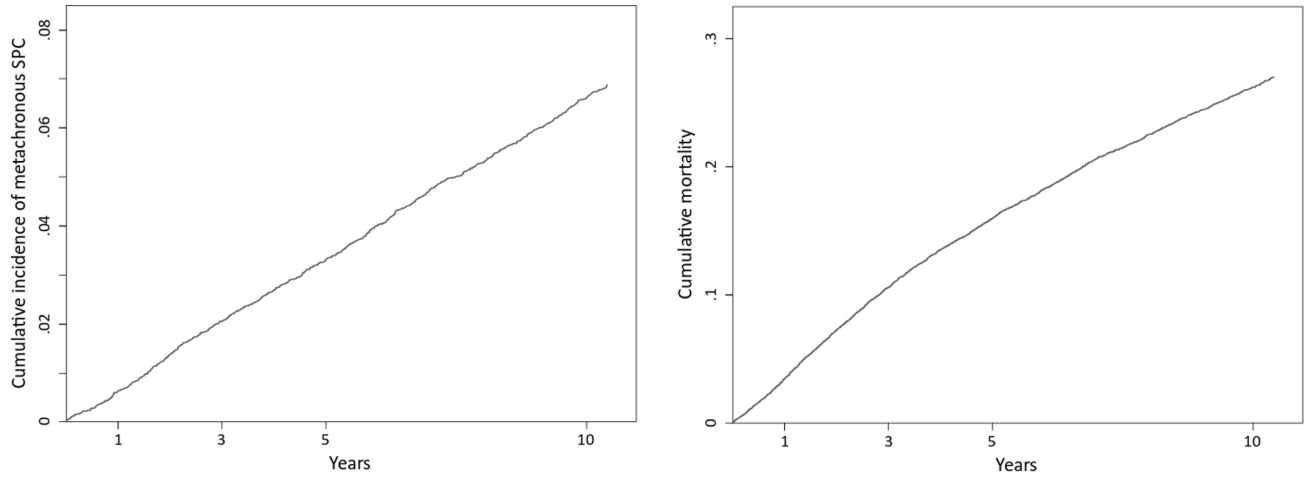

Fig. 4 Cumulative incidence of metachronous second primary cancers and death, considering the competing event of death, among females with a first primary breast cancer. SPC, second primary cancer. * Note that a different scale is used for the two outcomes

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

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10549-023-07224-3.

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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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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