Risk of second primary cancer among women with breast cancer: A population-based study in Granada (Spain)

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HIGHLIGHTS
• We examined risk of second primary cancers in women diagnosed with a first primary breast cancer in Granada (Spain).
• This is the first Spanish population-based study on this issue, comprising a total of 5897 breast cancer cases.
• Women diagnosed with breast cancer have higher second cancer incidence, although risk differs by age and second cancer site.

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ABSTRACT
Objective. The higher risk of developing new cancers in breast cancer survivors is a public health concern. Our aim was to examine risk of second primary cancers among women diagnosed with breast cancer.

Methods. We studied two cohorts of female cancer patients identified in a population-based cancer registry in Granada (Spain): women first diagnosed with a primary breast cancer (n = 5897) and those with a primary cancer in another site (n = 22,814), followed during 1985–2007 for second cancers and breast cancer occurrence, respectively. We used Standardized Incidence Ratios (SIRs) to estimate second cancer risk by age (<50 y, ≥50 y), time since diagnosis (≤5 y, >5 y) and calendar periods (≤1995, >1996). SIR for breast cancer was calculated in the second cohort.

Results. The risk of developing second cancers (n = 314) was 39% higher (95% CI = 1.23–1.54) among breast cancer patients, and particularly high among women under 50 (SIR = 1.96, 95% CI = 1.48–2.44). Excess risk for endometrial cancer (SIR = 3.04, 95% CI = 2.14–3.94) was statistically significant and remained so in women over 50. Younger women were at higher risk of second ovarian cancer (SIR = 4.90, 95% CI = 1.27–8.53). Increased SIRs were observed during the first five years after breast cancer diagnosis, whereas SIRs decreased thereafter. Breast cancer incidence (n = 171) was not higher among women previously diagnosed with other cancer types (SIR = 0.86, 95% CI = 0.74–1.00).

Conclusion. Women diagnosed with breast cancer have a higher incidence of second primary cancers, particularly of endometrial cancer in women over 50 at diagnosis, and ovarian cancer in younger women. These findings may be explained by treatment-related effects or shared risk factors.

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Introduction

Estimates of cancer incidence and mortality in Europe in 2012 show that breast cancer remains the most common cancer and cause of cancer-related death in women, with approximately 464,000 new cases diagnosed in 2012 [1]. In Spain, estimates suggest that 27,000 new breast cancers will be diagnosed by 2012 [2], breast cancer also being the leading cause of death from cancer [1].

According to EUROCASE studies, in Europe, the mean 5-year survival rate of women with breast cancer has increased from 76% in 1990–1994 to 79% in 1995–1999 [3,4]. Early detection of cancer, better access to care, and availability of adequate treatments may have led to improved survival rates [4].

From the late 1980s until the early 2000s incidence rates have also been rising in Spain, while mortality rates have declined since 1993.
Although the upward trend in incidence has been attributed to lifestyle changes, the decline in mortality [5–7] may be due to advances in cancer treatment and the consolidation of population-based screening programs. The long-term health of these women has become an important public health issue because the likelihood of developing a second primary cancer may be on the rise. Increased risk for Multiple Primary Tumors (MPT) has been related to various factors, such as a common etiology between cancers (i.e. genetic, environmental or hormonal factors), a consequence of breast cancer treatments, or even chance [8].

Several population-based cancer registry studies [9–19] and multicenter cancer registry studies [20,21] have shown that in comparison to the overall population, women diagnosed with a previous breast cancer have a higher risk of developing a second primary cancer. Elevated risks have been reported for the following cancer sites: endometrium [12,17,20], ovary [11,14,18–21], skin melanoma [16,21], stomach [11,20,21], colon and rectum [11,20,21], thyroid gland [14,16,18,20,21], lung [11,16,20,21], soft tissue sarcomas [11,21,21], and leukemias [11,15,16,20,21], among others.

Since incidence and mortality trends vary by age, age-differences in risk for second cancers are also plausible. Some studies have examined risk estimates by age groups [10,14–16,20,21]. Overall, women diagnosed with breast cancer at premenopausal age were at higher risk of developing a second primary non-breast cancer, with an excess increased risk ranging from 18% to as high as three- or four-fold. Distribution of cancer sites also appears to vary by age, but there is no consistency across studies. Risk estimations based on time since first breast cancer diagnosis have also yielded inconsistent results. In some studies risk increased during a short period after breast cancer diagnosis has also yielded inconsistent results. In other studies risk increased during a short period after breast cancer diagnosis [1 to 5 years] [9,14] while opposite findings were reported in others [12,20].

In Spain, risk of second primary cancers following a first primary breast cancer has not yet been evaluated at the population level. This study aims to assess the risk of second primary cancers in women diagnosed with a first primary breast cancer in Granada Province between 1985 and 2007, and examines the influence of age at diagnosis, time since diagnosis of the first primary cancer, and calendar periods. Additionally, to explore whether second primary cancers were caused by shared risk factors or by treatment side effects, the risk of breast cancer occurrence after a first primary non-breast cancer was also examined.

Methods

Population

The study population was derived from a population-based cancer registry located in southern Spain, the Granada Cancer Registry, covering 880,000 inhabitants (447,000 women) [22].

6020 women residing in Granada Province were diagnosed with an invasive first primary breast cancer between 1 January 1985 and 31 December 2007. Breast cancers were defined according to the International Classification of Diseases for Oncology, 3rd Edition, ICD-O-3 (code: C50). We excluded patients whose first primary cancer diagnosis and death were recorded simultaneously (Death Certificate Only, DCO cases, 1.9%) and synchronous first primary cancers (0.1%). 5897 women diagnosed with a first primary breast cancer constituted one cohort in this study.

The second cohort included 24,018 women diagnosed with a first primary non-breast cancer within the same study period. After excluding DCO cases (3.6%), synchronous first primary cancer cases (0.5%), and one case under age 15, the number of first primary non-breast cancer cases was 22,814.

Definition and coding of multiple primary tumors

Coding of multiple primary tumors followed a common set of rules proposed by the International Association of Cancer Registries (IACR) and the International Agency for Research on Cancer (IARC) (ICD-O-3) [23]. Accordingly, a primary cancer is one that originates in a primary site or tissue and is not an extension, nor a recurrence, nor a metastasis. MPT are those arising in different organs, and are identified through the three-character category or the topography of the ICD-O Those arising in the same organ, tissue or pair of organs are counted as only one tumor, unless the histology is different. For this reason, contralateral breast cancer is considered as a single tumor and was not included for risk assessments.

Variables and follow-up

The following variables were included in the analysis: a unique study number, date of birth, date of first primary cancer diagnosis, first primary cancer diagnosis (ICD-O-3), date of second primary cancer diagnosis, second primary cancer diagnosis (ICD-O-3), vital status and date of death.

All cases of first primary invasive breast cancer were followed up from the date of first breast cancer diagnosis until either the date of the second primary cancer, the date of death or the date of end of follow-up on 31st December 2007, whichever occurred first. Vital status was updated by linkage to the Spanish National Mortality Index and other sources, such as hospital discharge databases and clinical records.

Cases of various types of first primary non-breast cancer were also followed up for second primary breast cancer, with entry and exit dates defined as above.

Statistical analysis

Descriptive statistics included counts and percentages (%) for categorical variables and mean with standard deviations (SD) for continuous variables. T-tests for two independent samples were used to compare variables. Two-sided tests were applied using the 5% significance level.

To estimate second primary cancer risk, standardized incidence ratios (SIRs) and 95% confidence intervals (ICs) were obtained by comparing observed and expected cancer incidence rates, and assuming that the number of observed second primary cases followed a Poisson distribution [24]. Person-years at risk were used to calculate the estimated number of expected cases assuming a reference population with Spanish age-specific cancer incidence rates, published in Cancer Incidence in Five Continents Vol. IX [22]. SIRs were calculated only for cancer sites with more than 4 observed cases. Furthermore, we calculated the absolute excess risk (AER) to assess the excess incidence of overall second cancer, expressed as the excess number of second malignancies per 10,000 patients per year [19]. Since information on the women's menopausal status when diagnosed with breast cancer was unavailable, we used age at diagnosis as a proxy for menopausal status (women under age 50 were considered pre- and perimenopausal; women aged 50 and over were considered menopausal) [25].

SIR estimates were stratified according to age groups at diagnosis (<50 years vs. ≥50 years), by time since cancer diagnosis (<5 years vs. >5 years) and by calendar period at breast cancer diagnosis (1985–1995 vs. 1996–2007) in order to explore whether the risk of second cancers differed over the follow-up period.

The same approach was applied to examine the risk of developing a primary breast cancer subsequent to a first primary non-breast cancer, i.e. cancer cases were followed up for a second primary cancer in the breast. This analysis was performed to determine the plausible role of shared risk factors or treatment on the occurrence of second cancers. When no reverse association exists between breast cancer and another type of cancer, the association is most likely explained as a side effect of breast-cancer treatment.

Analyses were performed using the statistical software R, version 2.12.1.
Results

Second primary cancer after first primary breast cancer

5897 women were diagnosed with a first primary breast cancer in Granada Province during 1985–2007 and 314 of them subsequently developed a second primary cancer. Table 1 shows the distribution of these cases by age at diagnosis of the first primary breast cancer, calendar year, summation of person-years of follow-up and mean follow-up time. Of the 4170 women diagnosed with primary breast cancer at postmenopausal age (≥50 years), 251 were diagnosed with a second primary cancer. Mean age at first breast cancer diagnosis was 58.7 years, with statistically significant differences between women with a primary breast cancer (58.6 years) and those who later developed a second cancer (60.9 years). Differences were not statistically significant when this comparison was carried out within each age group, although mean age at diagnosis of the second primary cancer differed significantly between both age groups. About 52% of second primary cancer cases occurred within the first 5 years after breast cancer diagnosis. The number of second primary cancer cases decreased from 164 during 1985–1995 to 150 during 1996–2007.

Table 2 shows SIR and 95% CIs for second primary cancers by age groups and cancer site. Overall, women diagnosed with a first primary breast cancer had a 39% (95% CI: 1.23–1.54) higher risk of a second primary cancer compared with the general population. The excess incidence of second cancers was 23/10,000 patients/year (Supplementary Table 1). Risk was significantly higher for endometrial cancer and for non-melanoma skin cancer. The risk of a second primary cancer varied slightly with age for different cancer sites. The most frequent cancer sites in women under 50 were non-melanoma skin (38.1%), ovary (11.1%), colorectal (7.9%), stomach (6.3%) and the thyroid gland (6.3%). Among older women non-melanoma skin (33.5%), endometrial (16.5%) and colorectal cancer (10.8%) were more common. The increased risk of all second primary cancers combined was more pronounced in younger women (SIR = 1.96, 95% CI: 1.48–2.44) than in women over 50 (SIR = 1.29, 95% CI: 1.13–1.45). Risk of non-melanoma skin cancer was significantly higher in both age groups, while for endometrial cancer a significant increase in risk was observed only in the oldest age group (SIR = 3.06, 95% CI: 2.12–3.98). Women under 50 were at higher risk for ovarian cancer (SIR = 4.90, 95% CI = 1.27–8.53).

SIRs and 95% CIs by time since breast cancer diagnosis and calendar period are shown in Table 3. Risk increased 3.45-fold (95% CI = 2.92–3.98) in the first 5 years after diagnosis of the first primary breast cancer. After a first primary breast cancer, endometrial, ovarian, colorectal, bladder and non-melanoma skin cancer, as well as hematologic malignancies, were the cancer sites most likely to follow. The increased risk tends to disappear when more than 5 years have passed since breast cancer diagnosis, except for subsequent endometrial and non-melanoma skin cancer for which the risk remained statistically significant. Analyses by time since breast cancer diagnosis confirmed that the increase in risk is more pronounced in the earlier years following breast cancer diagnosis and less apparent after more than five years (Fig. 1). By calendar periods, the increase in risk of second primary cancers was fairly similar in both periods (1985–1995 and 1996–2007). SIR estimates were statistically significant only for endometrial and non-melanoma skin cancer, and higher in the second period (SIR = 3.15, 95% CI = 1.80–4.50 and SIR = 4.78, 95% CI = 3.55–6.01, respectively). SIR analyses by calendar year showed a progressive increase in accumulated SIR, reaching a maximum in the late 90s and remaining stable afterwards (data not shown).
Discussion

This is the first Spanish population-based study of second cancer risk among female breast cancer survivors. Using data from the Granada Cancer Registry (Southern Spain), it is based on nearly 6000 breast cancer cases followed for second primary cancers within the period 1985–2007. Women diagnosed with a first primary breast cancer in Granada had a 39% excess risk of developing a second primary cancer, in comparison with the general population of Spanish women. By age group, risk was notably higher in women under age 50 at diagnosis. The most frequent second primary cancer sites were the skin (non-melanoma tumors) and endometrium, though the distribution of second cancers varied by age. Endometrial and ovarian cancer were distinctive second cancers in women under 50 (3-fold increase risk) and women 50 and over (4.9-fold increase risk), respectively.

Several population-based studies have reported risk estimates of similar magnitude, ranging from 10 to 30% risk of developing second primary cancers [12,14,18–21]. Some studies considered contralateral breast cancer for risk estimations and are therefore not strictly comparable [9,13,15,16,19,26,27], although a similar tendency of higher risk of second primary cancers was observed. The most reliable risk estimate can be drawn from a multicenter study of Cancer Registries that used data from Europe, Canada, Singapore and Australia, which included a very high number of second cancer cases (n = 31,399) and long follow-up period (1943–2000). This study concluded that the increased risk of developing a second primary cancer was 25% (95% CI 1.24–1.26) higher than the expected increase in the general female population [20].

Overall, younger age at breast cancer diagnosis (<50 years) has been related to a higher second primary cancer risk, though estimates vary widely from 1.40 to 3.0 [10,14,20,21], or from 1.30 to 4.5 (including contralateral breast cancer) [9,13,15,16,19]. The higher risk of developing a second primary cancer in the ovary at young ages has also been reported in several studies [9–11,14–19]. This may be explained by genetic susceptibility to early-onset breast and ovarian cancers, based on germline mutations in the BRCA1/2 genes [28].

Shared reproductive risk factors between both breast and ovarian cancers, based on germline mutations in the BRCA1/2 genes [28]. Some studies have considered contralateral breast cancer for risk estimations and are therefore not strictly comparable [9,13,15,16,19,26,27], although a similar tendency of higher risk of second primary cancers was observed. The most reliable risk estimate can be drawn from a multicenter study of Cancer Registries that used data from Europe, Canada, Singapore and Australia, which included a very high number of second cancer cases (n = 31,399) and long follow-up period (1943–2000). This study concluded that the increased risk of developing a second primary cancer was 25% (95% CI 1.24–1.26) higher than the expected increase in the general female population [20].

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Table 3
Standardized incidence ratios (SIRs) and 95% CI for second primary cancers in women diagnosed with a first primary breast cancer, by time since first diagnosis and by calendar-year.

Table 4
Standardized incidence ratios (SIRs) and 95% CI for breast cancer development in women diagnosed with a first primary non-breast cancer.

Fig. 1. Standardized incidence ratios (SIRs) and 95% CI for second primary cancers after a first primary breast cancer, by year after diagnosis (dots and vertical bars). The line and shaded region represent the cumulative standardized incidence ratio and its 95% CI.

SIR was only calculated for cancer sites with more than 4 observed cases.

⁎ SIR of statistical significance (p < 0.05).
cancer may also play a role in this association [29,30]. Besides, the poorer prognosis of patients with ovarian cancer in comparison with breast cancer patients [4] may contribute to the lack of increased incidence of breast cancer among women with this type of tumor. For women 50 years or over at breast cancer diagnosis, several studies have noted a significant increase in risk for endometrial cancer as second primary cancer [10,14,16,20]. Tamoxifen therapy for breast cancer, used in cases expressing hormone-receptors and approved in Spain in the 90s may contribute to the observed association between both cancer sites [31]. However, the excess of endometrial cancer might not be entirely attributed to tamoxifen since endometrial cancer risk increased similarly in both calendar periods. Moreover, the increased risk remained significant after more than 5 years of follow-up. Hence, common risk factors are also likely to account for this excess risk. Breast and endometrial cancer also share common risk factors, such as obesity and reproductive factors [29,30,32]. It has also been reported that there is a reciprocally elevated risk between breast and ovarian or endometrial cancer, possibly suggesting the involvement of hormonal and/or genetic mechanisms [20]. We found no significant increase of breast cancer among women previously diagnosed with any of these two cancer sites, but could not stratify by age group due to the insufficient number of second breast cancer cases. However, we found that the risk of developing breast cancer after a first primary non-breast cancer was significantly elevated only among younger women, perhaps implying that genetic and environmental factors play a major role in this age group.

Our study showed a 4-fold increased risk in non-melanoma skin malignancies among women with breast cancer, a trend similarly observed by others [9–16,20,21]. We could estimate SIRs for non-melanoma skin cancer because these tumors have been systematically recorded in our cancer registry. Some studies have highlighted the side effects of therapeutic ionizing radiation, specifically confined to the site of radiation exposure, as a major cause of cancer [33]. Aside from adjuvant radiotherapy, chemotherapy produces severe immunosuppression which also may mediate the carcinogenic process. Our results point to the influence of breast cancer treatment side effects since no reverse association existed between both non-melanoma skin and breast cancer. We found no statistically significant elevated risks for the other cancer sites, although a few studies have reported elevated risk for some of them (stomach, colon and rectum, hematologic malignancies, etc.) [10,14,20,21]. An increased risk of subsequent thyroid cancer has been reported before, but reasons for this association are unclear [20,27]. We did not observe a significant increased risk, but interestingly, all cancer cases occurred in younger women.

Risk estimations by time interval between diagnosis of breast cancer and the second cancer, and on the year of diagnosis, may indicate whether the association is likely to be treatment-related [12,21]. In general, the risk of second cancers, specifically endometrial, colorectal, ovarian, non-melanoma skin, bladder cancer and hematologic malignancies, increased significantly in the five first years after breast cancer diagnosis, but not later, except for endometrial and non-melanoma skin cancer. This higher risk in the early years following breast cancer diagnosis coincides with some previous studies [9,14]. A plausible explanation for this increased risk is that second cancers may be more likely detected in women who were more recently diagnosed with breast cancer because they undergo regular cancer surveillance. This may have also driven the inverse association that was seen for second cancers diagnosed beyond five years of follow-up. When considering risk estimates by calendar years, incidence of second cancers was fairly similar. In other studies, a slight decrease in risk over the years was observed [12,20]. This has been attributed to differences in breast cancer therapies across countries and over recent decades [20], possibly affecting the interpretation and comparison of results. Our results suggest that risk of ovarian cancer is more inheritance-based (risk was maintained only during the first year after breast cancer diagnosis), and that endometrial cancer might be also subject to treatment and/or environmental factors (risk increased even after more than 5 years, possibly overcoming the cancer latency period).

Some limitations of our study should be considered. The low number of second cancer cases, particularly for less frequent cancer sites, constrained the analysis to few stratification variables. Information on treatment for breast cancer was unavailable, and the same is true regarding other variables which may play a role in the occurrence of second cancers, such as menopausal status, stage of breast cancer, hormone receptor status of the breast [34–36], family history or genetic susceptibility. Information on hysterectomy status was also unavailable and would have been particularly relevant to estimate SIRs for endometrial cancer, as those women who underwent a removal of the uterus are no longer at risk and may have biased these estimates towards the null. The influence of follow-up losses due to emigration of cancer patients is unlikely, as well as possible misclassification of metastases as a new primary cancer [37]. This study’s main strengths are that its results are population-based, the long follow-up of this study and the availability of information regarding non melanoma skin cancers, that have been recorded in the Granada Cancer Registry from the beginning of its activity.

This study shows that women with breast cancer are at increased risk of developing a second primary cancer compared with the general female Spanish population. Furthermore, women diagnosed with breast cancer at premenopausal ages are at higher risk of developing ovarian cancer, while women at postmenopausal ages are more prone to develop endometrial cancer. These increased risks may be related to adjuvant treatment side effects or to predisposing genetic and environmental factors. More research should focus on isolating the causes that may predispose a breast cancer survivor to develop a second cancer.

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Conflict of interest statement
The authors declare that they have no conflict of interest. Disclosures: none.

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