

Research Article

Gynaecological malignancies after breast cancer diagnosis: A population-based study

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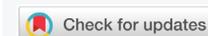
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Keywords: Breast cancer; Gynaecological malignancies; Second primary cancer; Standardized incidence ratio



Abstract

Background: Breast cancer (BC) is one of the most prevalent malignancies. BC survivors have higher risk of second primary cancers than the general population. There is an increased interest in BC survivor management, including the prevention of these second cancers. The aim of this study was to assess the risk of gynaecological malignancy (GM) as second neoplasm among BC patients in our population.

Methods: Patients with invasive BC diagnosed from 1980 to 2014 included in the Girona Cancer Registry were included. The incidence of second GM in these patients was compared to those in the general population. Second primary cancer was stated as a tumour diagnosed after 2 months from the BC diagnosis. Standardized incidence ratios (SIR) and absolute excess of risk (AER) were calculated.

Results: 9,717 patients were diagnosed with invasive BC during this period, with a median age at diagnosis of 61 years, and a median follow-up of 7.9 years. 117 of them developed a second GM. By tumour type, the only statistically significant higher SIR was observed for corpus uteri cancer (SIR:2.28 95% CI 1.82-2.83; AER:6.43 95% CI 4.13-9.14). After reviewing the histology of the corpus uteri cancer cases, we found that 71.4% were type I (endometrioid adenocarcinoma), 15.5% type II (serous adenocarcinomas and clear cell carcinomas), 10.7% carcinosarcomas, 2.4% sarcomas and there were no unspecified malignant neoplasms.

Conclusion: BC survivors have an increased risk of corpus uteri cancer, with an increase in unfavourable histologies compared to the general population. Lifelong primary and secondary prevention interventions should be recommended for these patients.

Introduction

Breast cancer (BC) is the most common diagnosed cancer and the leading cause of cancer death among women worldwide. It has been estimated that 2.1 million of new cases will be diagnosed in 2018. Based on rates from the GLOBOCAN 2018, 5.03% (one in 20) of women born today will be diagnosed with BC at some point during their lifetime [1].

In Catalonia, there has been a change in the epidemiology

of BC during the last 20 years. An increase of the incidence has been observed, achieving a crude rate of 118.6 cases per 100,000 women per year in 2015, but there has been a significant decrease in mortality since 1990 [2]. In Girona province, women diagnosed during the 2010-2014 period had a 5-years relative survival of 83.9% [3].

Although BC is the leading cause of death by cancer in women, advances in screening [4], diagnosis and therapeutic

approaches have improved its survival rate in the past decades. In light of this increased survival, the group of BC patients is exposed to a long-term risk of developing second malignancies. These second neoplasms are suggested to be related with the potential side effects of the treatment received (chemotherapy, radiotherapy and hormone therapy) [5], but also with shared risk factors with other malignancies [6]. In recent decades, there is an emerging awareness about survivors and their life quality. One of the main concerns is the study and application of health interventions in this group of patients to reduce the exposure to risk factors that lead to a second primary malignancy and to assure an early diagnosis in cases when a second cancer appears [7].

Many aetiological factors described for BC are also related to other types of cancer. There are non-modifiable risk factors such as gender, age or race [8]. Furthermore, early aged BC susceptibility genes like *BRCA1* and *BRCA2* can increase the risk of gynaecological malignancies (GM) such as ovarian and fallopian tube carcinomas [9], while *PTEN* and *P53* mutations are also related with ovarian and uterine (endometrial) cancers [10]. Modifiable, lifestyle-related risk factors for BC such as diet, obesity and hormone therapy after menopause are also risk factors described for endometrial cancer [6].

Several cancer registry-based studies and series that describe the incidence of second neoplasms among BC survivors have been published. Most of them reported an overall excess risk of about 20%-30% for second primary cancers (not including contralateral BC). The most consistent findings have been reported for sites like endometrium, ovary, thyroid gland, stomach, soft tissue sarcomas, blood and lung [11-16]. In addition to this, BC patients treated with tamoxifen presented an increased risk of endometrial cancer, and particularly those rare tumour types associated with poor prognosis [17].

On the other hand, some studies about women diagnosed with GM suggest that being previously diagnosed with BC could act as a risk factor to develop such GM [18]. Consequently, this association between breast and gynaecological cancers may indicate the need to establish specific guidelines for the diagnosis, treatment and follow-up of BC patients.

Based on the hypothesis that BC patients have an increased risk to develop GM, which may be related with shared risk factors and treatment side effects, the aims of this study were: 1) to analyse the incidence of second primary GM in a cohort of BC patients, 2) to assess this risk with the risk of developing a GM in the general population, in order to determine the excess risk in these patients, and 3) to compare the percent distribution of corpus uteri cancer histologies after BC with those that present the patients with corpus uteri cancer as a first primary tumour.

Material and Methods

In this retrospective cohort study, we used data from the

Girona Cancer Registry (GCR), a population-based cancer registry in the northeast of Spain that covers the Girona province (with a population of 756,156 people according to the census of 2014, source: Catalan National Institute of Statistics, IDESCAT). The GCR was established in 1980 as a monographic population-based registry for gynaecological and breast cancers. Since 1994 it includes information about all types of cancer. Its main information sources are the records of regional and community hospitals, the haematology and pathology departments, and death certificates.

Our study cohort included all women, aged 18 or more, who had a diagnosis of an invasive BC (codes from C50.0 to C50.9 of the 10th revision of the International Classification of Diseases ICD-10) over the period of 1980-2014. This cohort was followed until December 31st, 2014 in order to find all second primary invasive GM except contralateral BC. GM corresponds to codes C51 to C57 for malignant neoplasms of the vulva, vagina, cervix uteri, corpus uteri, uterus not otherwise specified (NOS), ovary and unspecified female genital organs. The inclusion or exclusion criteria of tumours as second primary cancers were defined following the IARC-IACR recommendations for the definition of multiple primary cancers.

The observed incidence of second GM in our cohort of patients was compared against the expected incidence of these tumours in the reference population. Standardized Incidence Ratios (SIR) were calculated dividing the observed second GM among the BC patients cohort by the expected number of GM based on population rates. In order to validate the study's hypothesis, it was assumed that the observed number of second GM cases followed a Poisson distribution. All the analyses were computed using R software. The observed number of cases included all second GM diagnosed in the patient's cohort.

To estimate the expected number of cancers, the 5-year age group, period (1980-1984, 1985-1989, 1990-1994, 1995-1999, 2000-2004, 2005-2009, and 2010-2014) and site-specific incidence rates (extracted from the GCR) were multiplied by the number of accumulated person-years at risk (PYO).

The PYO was defined as the number of years from the date of first BC diagnosis to date of second GM, date of death or end of follow-up (December 31st, 2014), whichever date came first, and was calculated using the person-years and mortality computation programme (PAMCOMP).

The excess absolute risks (EAR) beyond the expected ones were calculated subtracting the expected number of subsequent cancers from the observed number of cases of cancer and dividing the difference by the observed person-years and expressing the number of cases in excess or deficit by 100,000 person-years.

The SIRs were evaluated by each GM tumor type and all GM (C51-C57) using the International Classification of Diseases, 10th edition (ICD-10). The first two months after the first cancer diagnosis were considered as a synchronous period and the SIRs were computed both excluding and including the observed and the expected cases during this period.

With the aim of comparing corpus uteri cancer histologies after breast cancer with those of corpus uteri cancer as first primary tumors, five different histological classification groups of corpus uteri cancer were used in this study (Table 1). The classification used follows the WHO Classification of tumours of the corpus uteri. The five groups were: 1) epithelial tumours type I (endometrioid carcinoma, adenocarcinoma NOS and adenocarcinoma with squamous differentiation), 2) epithelial tumours type II (serous/papillary serous and mixed

cell adenocarcinoma) following the indications of different endometrial cancers reports [19], 3) mesenchymal tumours, 4) mixed epithelial and mesenchymal tumours and 5) others tumours of the uterine corpus. All corpus uteri cancer with an unspecified histological diagnosis were reviewed in order to include each of them in one of these five histological groups. Furthermore, all histological samples of cases classified as carcinosarcoma were reviewed by a pathologist to validate the diagnosis. Then, the frequency and distribution of histological groups by first or second corpus uteri cancer was described and a Chi-squared test for statistical inference was performed. A missing completely at random pattern was assumed and thus a complete case analysis was performed.

Results

The study included 9,717 cases of BC diagnosed between 1980 and 2014 with one month or more of follow-up yielding 76,764 PYO (Table 2). The median age at diagnosis of primary BC was 61 (range = 18-102) years. A total of 117 second primary GM were diagnosed in our cohort (1.20% of patients) versus 76.8 expected in the reference population (SIR 1.52; 95% CI 1.26-1.83, EAR 5.41/100,000 person-years) (Table 3). The median age among patients diagnosed with a second GM after BC was 67.5 (range = 34-89) years, with a median duration between the diagnosis of BC and the diagnosis of the GM of 5.88 (range = 0-23) years. The mean follow-up time was 7.90 (range = 0-26) years.

The most common observed second GM was corpus uteri cancer, with 84 cases diagnosed versus 37.21 expected (SIR 2.28; 95% CI 1.82-2.83; AER 6.43/100,000 PYO). We also

Table 1: Histological classification of tumours of the corpus uteri.

	ICD03	Histological Classification
1 Type I, Endometrioid adenocarcinomas		
	8070	Squamous cell carcinoma, NOS
	8071	Squamous cell carcinoma, keratinizing, NOS
	8140	Adenocarcinoma, NOS
	8211	Carcinoma tubular
	8262	Villous adenocarcinoma
	8380	Endometrioid adenocarcinoma
	8383	Endometrioid adenocarcinoma, ciliated cell variant
	8384	Adenocarcinoma, endocervical type
	8480	Mucinous adenocarcinoma
	8481	Mucin-producing adenocarcinoma
	8560	Adenosquamous carcinoma
	8570	Adenocarcinoma with squamous metaplasia
	8934	Carcinofibroma
2 Type II, Serous adenocarcinomas and clear cell carcinomas		
	8020	Carcinoma, undifferentiated, NOS
	8260	Papillary adenocarcinoma, NOS
	8310	Clear cell adenocarcinoma, NOS
	8323	Mixed cell adenocarcinoma
	8441	Serous cystadenocarcinoma, NOS
	8460	Papillary serous cystadenocarcinoma (C56.9)
	8461	Serous surface papillary carcinoma (C56.9)
3 Mesenchymal tumours		
	8800	Sarcoma, NOS
	8890	Leiomyosarcoma
	8891	Leiomyosarcoma, epithelioid variant
	8896	Leiomyosarcoma, myxoid variant
	8930	Undifferentiated endometrial sarcoma
	8931	Endometrial stromal sarcoma, low grade
	8935	Stromal sarcoma, NOS
	9110	Mesonephroma, malignant
4 Mixed epithelial and mesenchymal tumours		
	8933	Adenosarcoma
	8950	Mullerian mixed tumour (C54.~)
	8951	Mesodermal mixed tumour
	8980	Carcinosarcoma
5 Others		
	8010	Carcinoma, NOS
	8012	Large cell carcinoma, NOS
	8030	Giant cell and spindle cell carcinoma
	8230	Solid carcinoma, NOS

Table 2: Descriptive characteristics of the Girona breast cancer cohort.

	N	(%)
Breast cancer cohort patients (1980-2014)		
	9,717	100
Age at diagnosis of breast cancer		
Mean	61.05	-
Median	61	-
<50 y	2,503	25.8%
≥50y	7,250	74.6%
Years of breast cancer diagnosis		
1980-1984	672	6.9%
1985-1989	914	9.4%
1990-1994	1,143	11.8%
1995-1999	1,393	14.3%
2000-2004	1,683	17.3%
2005-2009	1,832	18.9%
2010-2014	2,080	21.4%
Follow-up time (years)		
Mean	7.9 y	-
Median	5.88 y	-
Interval between diagnosis of breast and second gynaecological malignancies		
<1 y	1,260	13.0%
1-4 y	3,089	31.8%
5-9 y	2,367	24.4%
10-14 y	1,422	14.6%
>15 y	1,579	16.2%

y: years.

observed 3 patients diagnosed with vulva cancer versus 5.67 expected (SIR 0.53; 95%CI 0.10-1.57; AER -0.36/100,000 PYO); 1 case of vaginal cancer versus 0.85 expected (SIR 1.17; 95% CI 0.00-6.73; AER 0.02/100,000 PYO); 5 cases of cervical cancer versus 9.84 expected (SIR 0.51; 95% CI 0.16-1.20; AER -0.65/100,000 PYO); 19 cases of ovarian cancer versus 19.89 expected (SIR 0.96; 95% CI 0.57-1.49; AER -0.12/100,000 PYO) and 5 cases of other and unspecified female genital organs cancers versus 1.46 expected (SIR 2.73; 95% CI 0.71-7.07; EAR 0.34/100,000 PYO) (Table 3).

Between 1st January 1980 and 31st December 2014, 1,661 women were diagnosed with corpus uteri cancer in the Girona province. Table 4 shows the distribution of the morphologies according to the five groups. Most women had type I adenocarcinomas (84.5%) while the 7.5% of them had type II adenocarcinomas, 3.6% mixed epithelial and mesenchymal tumours, 3.4% mesenchymal tumours and 0.7% others. The distribution of histologies of corpus uteri cancer after BC was different from those of corpus uteri cancer as first primary tumour. Among the 84 cases of corpus uteri cancer after BC, 71.8% were type I adenocarcinoma, 15.3% type II adenocarcinoma, 10.6% mixed epithelial and mesenchymal tumours, 2.4% mesenchymal tumours and there were no cases of unspecified malignant neoplasms. Despite the lack of information on the histologic subtype of approximately 20% of the samples, we observed a higher proportion of high-risk histologies (adenocarcinoma type II and Mixed epithelial and mesenchymal tumours) among corpus uteri cancer which were second neoplasm.

Table 3: Age-standardized incidence ratios (SIR) and excess absolute risk (EAR) of gynaecological malignancies after breast cancer (excluded first 60 days after breast cancer diagnosis) from 1980 to 2014 in Girona.

Second gynaecological malignancies	OBS	EXP	SIR	95% CI (SIR)	EAR	95% CI (EAR)
Vulva (C51)	3	5.67	0.53	(0.10-1.57)	-0.36	(-0.69-0.43)
Vagina (C52)	1	0.85	1.17	(0.00-6.73)	0.02	(-0.11-0.66)
Cervix uteri (C53)	5	9.84	0.51	(0.16-1.20)	-0.65	(-1.11-0.26)
Corpus uteri (C54)	84	37.21	2.28*	(1.82-2.83)*	6.43	(4.13-9.14)*
Uterus, unspecified (C55)	0	1.87	0.00	(0.00-2.09)	-0.25	(-0.25-0.28)
Ovary (C56)	19	19.89	0.96	(0.57-1.49)	-0.12	(-1.14-1.32)
Other and Unspecified female genital organs (C57)**	5	1.46	2.73	(0.71-7.07)	0.34	(-0.06-1.19)
Total (C51-C58)	117	76.8	1.52*	(1.26-1.83)*	5.41	(2.69-8.53)*

**C57 included Fallopian tube, broad ligament, round ligament, parametrium, uterine adnexa, other specified parts of female genital organs and overlapping lesion of female genital organs. CI: Confidence Interval

Table 4: Comparison of the histological group distribution according to the 2014 WHO classification between corpus uteri cancer as first tumour and corpus uteri cancer after first primary breast cancer. Girona, 1980-2014.

Histological group	Corpus uteri Total		Corpus uteri 1 st		Corpus uteri 2 nd		p - value*
	N	%	N	%	N	%	
Adenocarcinomas type I	1403	84.5%	1343	85.2%	60	71.8%	p < 0.001
Adenocarcinomas type II	124	7.5%	111	7.0%	13	15.3%	p = 0.008
Mixed epithelial and mesenchymal tumours	60	3.6%	51	3.2%	9	10.6%	p = 0.002
Mesenchymal tumours	63	3.8%	61	3.9%	2	2.4%	p = 0.37
Others	11	0.7%	11	0.7%	0	0.0%	p = 0.56
Total	1661	100.0%	1577	100.0%	84	100.0%	

Discussion

The number of BC survivors has increased due to the advances in earlier detection and treatment, as well as in supportive care. Thus, the risk of second primary cancers after a BC has become clinically more relevant. Second primary malignancies may reflect several factors such as an increased surveillance that can lead to an overdiagnosis, a previous received therapy being the cause of the second malignancy, and shared genetic or environmental risk factors between the first and second cancer [6,20].

This study confirms the existence of an excess of GM following the diagnosis of BC. Globally, we observed 117 second GM with a statistically significant high SIR (52% increased risk) which is caused by a high SIR in corpus uteri cancer (128% increased risk). Approximately, 5.41 extra cases of GM per 100,000 women per year occurred among women who suffered BC.

Previous studies have suggested that women with a BC history have an elevated risk of developing a second GM(5,7). In a cohort of 9,729 BC Swiss patients followed from 1974 until 1998, Levy et al found greater risk of developing a second corpus uteri cancer and a second ovarian cancer (SIR 1.47 95% CI 1.09-1.94 and SIR 1.26 95% CI 0.85-1.79 respectively), but a lower risk of cervical cancer (SIR 0.52 95% CI 0.21-1.06) [21]. Soerjomataram et al. found a 40% increased risk of developing a second corpus uteri cancer and a 70% increased risk of an ovarian cancer based on 9,919 BC Dutch patients over a period of 28 years (1972-2000). Further, they also observed a decrease by 10% of the cervical cancer risk among these patients [14]. One of the most important reports in number of patients (525,527) and follow-up period (1943-2000) was published by Mellekjaer, et al. [11]. They included women from several countries with primary BC identified from 13 population-based cancer registries. They also found an excess risk of endometrial and ovarian cancers (SIR 1.52 and SIR 1.48 respectively) and a lower risk of cervical cancer (SIR 0.94). Other studies obtained statistically significant higher SIRs of corpus uteri cancer and ovarian cancer in Slovenia [12], Connecticut [13], Turkey [15] and other geographical areas. On the other hand, some studies have described an elevated risk also for cervical cancer. In 1997, Volk and Pompe-Kirn, in a Slovenian cohort of 8,917 BC patients diagnosed between 1961 and 1985 and followed-up to the end of 1994, found an increased risk of corpus uteri cancer (60%), and ovarian (130%) and cervical cancers (10%) [12]. Differences in the risk of cervical cancer can be explained by the different time and degree of implementation of screening programmes for this cancer.

In agreement with previous reports, the main finding of this analysis is the excess of corpus uteri cancer in women diagnosed with invasive BC. Endogenous hormones, a shared risk factor for both BC and corpus uteri cancer, and exogenous hormones, related with hormone therapy for BC, could explain this finding. In addition, this excess of risk could be



also explained by a surveillance bias after the diagnosis of BC and by the tamoxifen treatment, since it is related with the development of endometrial hyperplasia and cancer [22].

Tamoxifen is a selective oestrogen receptor modulator. It has an anti-oestrogenic effect on breast tissue and an oestrogenic (carcinogenic) effect in the endometrium, resulting in the development of atrophy, hyperplasia, polypus and endometrial carcinoma [23]. It has been widely used during the last 40 years as adjuvant treatment in BC, for both premenopausal and postmenopausal women. Incidence results of second endometrial cancers after a long-term follow-up in studies on adjuvant hormonal therapy have been reported in the literature [17,24]. Multiple epidemiological studies and randomized prospective trials have shown an increased risk of endometrial cancer in association with prolonged tamoxifen treatment, with relative risks ranging from 2.53 to 7.5. It was also stated that there is an increased risk of developing uterine cancer among women receiving tamoxifen [25]. This finding has led to a major surveillance of these patients. Guidelines recommend surveillance with ultrasonography for patients receiving tamoxifen, despite its known low efficiency. There is also a strong recommendation to conduct a study with endometrial samples in patients who experience bleeding [26]. Recent result updates of one of the largest trials about adjuvant hormone therapy comparing 10 with 5 years of adjuvant tamoxifen (ATLAS trial) have been reported where an increase of the cumulative risk of endometrial cancer and specific mortality in postmenopausal women treated with tamoxifen has been found [24].

We detected a slight increase of unfavourable corpus uteri cancer histologies compared to those of the general population. An increased incidence of more aggressive histologies such as sarcomas has also been reported. In some case series, tamoxifen has been related to more aggressive histologies of corpus uteri cancer, such as uterine sarcoma [27] and high-grade uterine carcinoma [28]. More recently, a case-control study with 813 patients who developed endometrial cancer after a BC diagnosis showed an increased risk of endometrial cancer after treatment with tamoxifen for both premenopausal and postmenopausal women, which was statistically significant during and until 5 years after completing the treatment [29]. Another case series of 363 endometrial cancer patients showed that patients who develop an endometrial cancer after BC diagnosis showed worst prognostic, especially those who received tamoxifen, compared to patients without past medical history of BC [22]. In contrast, another recent report on the final results of the ATLAS trial showed higher cumulative risk of endometrial cancer, increasing with the treatment period length but outweighed by the risk of breast cancer mortality in hormone receptor positive patients [24].

Regarding ovarian cancer, in contrast to previous reports, our study found a non-statistically significant SIR (0.96; 95%CI 0.57-1.49). However, these other studies found a trend for an increased incidence of ovarian cancer which can be explained

by shared inherited susceptibility genes such as *BRCA1* and *BRCA2* [9]. Both cancers are related, but only significantly in this order, ovary after breast, and not the other way around [8].

Even though the number of observed cases of cervical cancer is limited, our results are consistent with previous studies, showing a decreased risk among BC patients. This lower risk may be explained by the introduction of the cervical cancer screening programme in our National Health Service in 1993, routinely performed in patients with breast cancer who are under the surveillance of gynaecological teams [30].

The strengths of our study are the population-based design based on data of a cancer registry, and the large and complete follow-up of patients. Cancer registries are the only tool to assess the risk of second malignancies due to its completeness and follow-up of all patients.

The limitations are the lack of information about risk factors and received treatments, which could allow us to study their relations with the development of second tumours in our cohort, as well as data on the patients who had undergone oophorectomy or hysterectomy for other reasons. This information is usually not recorded in cancer registries.

Some gynaecological cancers, such as the vulvar and vaginal ones, and those registered as unspecified, such as primary Fallopian tube cancer, are rare. This fact, together with the lack of individual data on risk factors and treatments, makes it difficult to estimate how much of the excess risk might be associated with shared lifestyle or genetic factors, and how much could be related to the received treatment for the initial BC. The excess of risk could also be explained, as mentioned before, by the increased surveillance of these patients or their general susceptibility to cancer.

Conclusion

In conclusion, our results found that women already diagnosed with invasive BC have an increased risk of developing a second primary corpus uteri cancer compared to the general population, with a slight increase in histologies of worse prognosis. Lifelong primary and secondary prevention interventions should also be recommended for these patients. More detailed investigation on the risk factors related to these findings and its implication to BC patients' survival is warranted.

Ethic Aspects

This is a descriptive study based on anonymised data collected by the GCR. Informed consent was not requested because no work was performed with medical records or biological samples.

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