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Risk for second primary non-breast cancer in pre- and postmenopausal women with breast cancer not treated with chemotherapy, radiotherapy or endocrine therapy

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ABSTRACT

Introduction: We investigated the risk for a second primary cancer in pre- and postmenopausal women with breast cancer treated by surgery alone, to assess the importance of non-treatment factors and menopausal status.

Patients and methods: The cohort comprised 14,151 women with breast cancer diagnosed during 1977–2006, who did not receive radiotherapy or systemic adjuvant therapy. They were identified in the nationwide clinical database of the Danish Breast Cancer Cooperative Group. The women were followed for a second primary cancer other than breast cancer in the Danish Cancer Registry, and risk was quantified as standardised incidence ratios (SIRs).

Results: Women with breast cancer diagnosed before menopause had an 18% greater overall risk for a second primary non-breast cancer than the general female population (95% confidence interval [CI], 1.06–1.32). The excess was confined to cancers of the endometrium (1.5; 95% CI, 1.0–2.0) and ovaries (1.8; 95% CI, 1.2–2.4). Rare histological subtypes of breast cancer were associated with these two cancer sites. Women with breast cancer after menopause had no overall excess risk for a second cancer (SIR, 0.98; 95% CI, 0.92–1.04).

Conclusion: An excess risk for second non-breast cancers related to non-treatment factors is seen primarily in breast cancer patients who were premenopausal at diagnosis.

1. Introduction

Breast cancer is the most commonly diagnosed cancer in women in developed countries.[1] In Europe, the mean 5-year relative survival of women with breast cancer increased from 76% in 1990–1994 to 79% in 1995–1999.[2] The improved prognosis and the high incidence of breast cancer result in increasing numbers of survivors; therefore, the long-term health of these women is an important public health issue.

Several studies have shown that women with a previous breast cancer have a higher risk for a second primary cancer than the general population.[3–11] An important question is how much of the excess risk can be ascribed to breast cancer treatment and how much to common genetic and environmental risk factors. Studies that included information on treatment provide estimates of the risk for a second cancer associated with radiotherapy,[3,4,8–12] chemotherapy and hormonal therapy;[3,11,12] however, few investigated the risk for a second primary cancer in women who underwent surgery alone.[9,10,12]

Differences in both risk factors[13,14] and prognosis[15,16] indicate that different breast cancer subtypes, as defined e.g. by

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gene expression, are unevenly distributed in pre- and postmenopausal women. Therefore, it is likely that pre- and postmenopausal breast cancer also predispose differently to a second cancer. We investigated the risk for a second cancer separately in pre- and postmenopausal patients with breast cancer treated only with surgery according to the nationwide clinical database of the Danish Breast Cancer Cooperative Group (DBCG).

2. Patients and methods

Since 1977, information on breast cancer patients in Denmark has been reported to the database of the DBCG, which contains information on menopausal status, tumour characteristics and treatment.[17] Patients are allocated to different treatment programmes on the basis of guidelines developed over time by the DBCG. Patients who are not included in the programmes are mainly those with distant metastases, previous malignancy, bilateral or inflammatory breast cancer, other medical conditions or old age (upper age limit depends on DBCG programme). Patients who are to be allocated to treatment are categorised into high- and low-risk groups on the basis of auxiliary lymph node status, tumour size, grade of malignancy, hormone receptor status and age. Categorisation in the low-risk group has consistently required lymph node negativity, while the cut-off point for tumour size has changed over time (Table 1). Grade of malignancy of ductal carcinomas, receptor status and age were added as risk group criteria in programmes initiated in 1989–2001. Patients in the low-risk group undergo mastectomy or breast-conserving surgery and radiation of the residual breast, while patients in the high-risk group receive additional postoperative radiotherapy and systemic adjuvant therapy according to different guidelines. Over time, as more criteria were added, more patients were allocated to the high-risk group; accordingly, more patients have received radiotherapy and systemic adjuvant therapy in recent years.[17]

From the DBCG database, we identified 15,290 women in the low-risk group who received surgery alone according to DBCG guidelines between 1st January 1977 and 31st December 2006. Thus, low-risk patients undergoing breast conserving surgery who received radiotherapy were not included. The following variables were obtained from the database: date of diagnosis of first invasive breast cancer, age and menopausal status at breast cancer diagnosis, histological type of tumour, receptor status and event date (date of loco-regional or distant recurrence or second breast cancer). The monitoring by DBCG for each woman continued up to 10 years after first breast cancer diagnosis unless a change in disease status, e.g. recurrence, had occurred earlier. Information on oestrogen receptor (ER) and progesterone receptor (PR) status was combined in the receptor status variable: if either ER or PR was positive, receptor status was defined as positive. Definition of menopausal status in DBCG programmes includes the following variables: length of menostasia as well as prior hysterectomy, bilateral oophorectomy and menstruation during cyclic hormonal therapy combined with a lower age limit. The definition has varied over the years in the different DBCG programmes, e.g. in relation to the length of menostasia and the lower age limit. More detailed information on definition of menopausal status can be found in Moller et al.[17] We excluded 15 women of unknown menopausal status.

The unique identification number given to all residents in Denmark by the Central Population Registry was used to link the cohort to the Danish Cancer Registry, a nationwide registry that includes virtually all cases of cancer in Denmark since 1943. The Registry receives data from hospital departments, pathology departments, physicians and death certificates.[18,19] Before 1978, cancers were coded according to a revised version of the International Classification of Diseases, 7th revision (ICD-7) codes. All cancer diagnoses in the Registry during 1978–2003 have been systematically converted to ICD-10 codes on the basis of topography and morphology codes in the International Classification of Diseases for Oncology, 1st

Table 1 – Overview of the criteria used for definition of low-risk breast cancer patients in the Danish Breast Cancer Cooperative Group (DBCG) programmes covering different time periods.

DBCG programme	Low-risk criteria in DBCG programmes				
	Lymph node status	Tumour size	Histology and grade	Receptor status[a]	Age at breast cancer diagnosis
DBCG 77 and 82	Negative	⩽5 cm			
DBCG 89[b]	Negative	⩽5 cm	***Grade I if ductal***[c]		
DBCG 99[b]	Negative	**⩽2 cm**	***Grade I if ductal***[d]	***Positive/unknown***	
DBCG 01[b]	Negative	⩽2 cm	Grade I if ductal	Positive/unknown	**⩾35 years**
DBCG 04[b]	Negative	⩽2 cm	Grade I if ductal	Positive/unknown	⩾35 years
DBCG 07	Negative	⩽2 cm	***Grade I if ductal or grade I–II if lobular***	Positive/unknown	⩾35 years
DBCG 10	Negative	⩽2 cm	Grade I if ductal or grade I–II if lobular	Positive/unknown	**⩾50 *years***

Boldfacing indicates a change in risk factor. The region marked below the line indicates risk factors not related to our study population included during 1977–2006.

[a] If either oestrogen or progesterone receptors were positive, the receptor status was defined as positive.

[b] Postmenopausal women ⩾70 years with high risk criteria are included in our cohort of women treated with surgery alone in DBCG programmes 89, 99, 01 and 04.

[c] Premenopausal women only.

[d] Both pre- and postmenopausal women.

and 3rd editions (ICD-O-1 and ICD-O-3). Since 2004, all cancer diagnoses have been reported in ICD-10 codes. The variables obtained from the Cancer Registry were date of second primary cancer, ICD-10 codes and vital status. Vital status is updated yearly by linkage to the Central Population Register. All types of cancer were included except non-melanoma skin cancer and second breast cancer. Bilateral breast cancers with similar histology are flagged in the Cancer Registry, but the date of diagnosis for the second breast cancer is not entered into the electronic version of the Cancer Registry, so it was not possible to follow the patients for a second breast cancer.

Follow-up began 12 months after the date of diagnosis of the first invasive breast cancer and ended on the date of diagnosis of the second primary cancer, the event date (date of recurrence or second breast cancer), the date of death, the date of emigration or the end of follow-up on 31st December 2007. The event date was inserted as a censoring date, because a patient may receive treatment other than surgery for a recurrent or second breast cancer. Since follow-up started 1 year after the breast cancer diagnosis, 1124 women were excluded because their exit date was within 1 year of their breast cancer diagnosis. Thus, the final cohort included in the analyses consisted of 14,151 1-year breast cancer survivors.

2.1. *Statistical methods*

The risk for a second primary cancer of women who received surgery alone for their breast cancer was described by standardised incidence ratios (SIRs), defined as the observed number of second cancers at each site divided by the expected number in women in the general population of Denmark. The expected number was calculated by multiplying the number of person–years at risk stratified by age (5-year intervals) and calendar period (5-year intervals) with cancer incidence rates for women in the general population in corresponding strata, and then summing across strata. The incidence rates for women in the general population were primary rates, including only the first tumour for each woman. The 95% confidence intervals (CIs) for SIRs were determined by assuming a Poisson distribution of observed second primary cancers using Byar's approximation.[20] All analyses were stratified on menopausal status. In addition, stratified analyses were carried out for age at breast cancer diagnosis, latency, DBCG programmes as well as histological type and receptor status of the breast cancer. A test for trend of the SIRs by latency was performed assigning the latency intervals the following values (1–4 years = 1, 5–9 years = 2, 10+ years = 3). The Bonferroni correction was used as a supplement in the evaluation of the SIR estimates.

3. Results

At the time of the first breast cancer diagnosis, 4269 (30%) women in the study population were premenopausal and 9882 (70%) were postmenopausal. The premenopausal patients contributed an average of 12.5 years of follow-up during the time period 1–30 years after breast cancer diagnosis, and the postmenopausal patients contributed an average of 9.0 years during a similar time period. Few premenopausal women with breast cancer were over 55 years of age, and less than 1% of postmenopausal women were under 45 years (Table 2). The proportion of premenopausal patients was highest in DBCG programme 82, while the proportion of postmenopausal patients was highest in DBCG programme 89. Regardless of menopausal status, the majority of women had invasive ductal carcinoma and positive or unknown receptor status.

The women with premenopausal breast cancer had a significantly elevated risk for all second cancers combined, with an SIR of 1.18 (95% CI, 1.06–1.32), while the SIR for postmenopausal women was 0.98 (95% CI, 0.92–1.04) (Table 3). For premenopausal women, the overall excess risk decreased with time since their breast cancer diagnosis, from an SIR of 1.34 (95% CI, 0.97–1.80) within 1–4 years of diagnosis to an SIR of 1.26 (95% CI, 0.99–1.57) for 5–9 years and 1.14 (95% CI, 0.99–1.30) after 10 or more years, but there was no statistically significant trend ($p = 0.26$). For postmenopausal women, the risk remained around unity in all three periods (data not shown). A significantly elevated risk for cancer of the ovaries and a

Table 2 – Characteristics of 14,151 1-year survivors with a first invasive breast cancer who underwent surgery alone during 1977–2006 in Denmark, stratified by menopausal status.

Characteristics	Menopausal status at breast cancer diagnosis			
	Premenopausal		Postmenopausal	
	No.	%	No.	%
All	4269	100	9882	100
Age at first breast cancer (years)				
<40	706	17	1	<1
40–44	1039	24	17	<1
45–49	1500	35	174	2
50–54	894	21	1079	11
55–59	128	3	2044	21
60–64	1	<1	2240	22
⩾65	1	<1	4327	44
DBCG programmes				
77	981	23	1717	18
82	1941	45	2165	22
89	1019	24	4768	48
99	177	4	512	5
01	69	2	307	3
04	82	2	413	4
Histological type				
Ductal	3268	76	7718	78
Lobular	497	12	1106	11
Medullary	122	3	177	2
Tubular	146	3	215	2
Other	236	6	666	7
Receptor status[a]				
Positive	1789	42	5358	54
Negative	362	8	1523	16
Unknown	2118	50	3001	30

[a] If either oestrogen or progesterone receptors were positive, the receptor status was defined as positive.

Table 3 – Observed (Obs) and expected (Exp) numbers of second primary cancers and standardised incidence ratios (SIRs) among pre- and postmenopausal 1-year survivors with a first invasive breast cancer who underwent surgery alone during 1977–2006 in Denmark.

Site of second primary cancer	Menopausal status at breast cancer diagnosis							
	Premenopausal				Postmenopausal			
	Obs	Exp	SIR[a]	95% Confidence interval (CI)	Obs	Exp	SIR[a]	95% CI
All (except second breast cancer)	343	289.7	1.18	1.06–1.32	943	963.3	0.98	0.92–1.04
Buccal cavity and pharynx	3	6.6	0.5	0.1–1.3	22	17.4	1.3	0.8–1.9
Digestive organs	83	69.0	1.2	1.0–1.5	315	301.2	1.1	0.9–1.2
Oesophagus	2	2.7	0.8	0.1–2.7	10	10.5	1.0	0.5–1.8
Stomach	8	5.1	1.6	0.7–3.1	22	22.9	1.0	0.6–1.5
Colon, including rectosigmoideum	34	29.9	1.1	0.8–1.6	134	138.4	1.0	0.8–1.2
Rectum	23	15.3	1.5	1.0–2.3	73	57.9	1.3	1.0–1.6
Gall-bladder and biliary tract	1	2.5	0.4	0.0–2.3	22	13.2	1.7	1.1–2.5
Respiratory system and intrathoracic organs	61	57.3	1.1	0.8–1.4	175	172.3	1.0	0.9–1.2
Lung	57	53.9	1.1	0.8–1.4	170	162.3	1.1	0.9–1.2
Melanoma	13	16.5	0.8	0.4–1.4	28	33.0	0.9	0.6–1.2
Mesothelium, connective tissue and bone	1	2.4	0.4	0.0–2.3	10	7.1	1.4	0.7–2.6
Female genital organs	85	62.1	1.4	1.1–1.7	136	165.6	0.8	0.7–1.0
Cervix uteri	10	13.1	0.8	0.4–1.4	12	25.5	0.5	0.2–0.8
Corpus uteri	36	24.6	1.5	1.0–2.0	62	72.6	0.9	0.7–1.1
Ovary	38	21.6	1.8	1.2–2.4	47	55.8	0.8	0.6–1.1
Urinary tract	26	19.6	1.3	0.9–1.9	68	74.9	0.9	0.7–1.2
Urinary bladder	18	11.6	1.6	0.9–2.5	40	44.3	0.9	0.6–1.2
Eye, brain and other parts of CNS[b]	21	17.5	1.2	0.7–1.8	43	40.8	1.1	0.8–1.4
Endocrine glands	3	2.6	1.2	0.2–3.4	3	5.5	0.5	0.1–1.6
Lymphatic and haematopoietic tissue	28	22.7	1.2	0.8–1.8	90	81.6	1.1	0.9–1.4
Leukaemia	9	7.0	1.3	0.6–2.4	23	28.5	0.8	0.5–1.2
Ill-defined and unspecified cancer	19	12.9	1.5	0.9–2.3	53	62.8	0.8	0.6–1.1

[a] None of the SIR estimates were statistically significant after the Bonferroni correction ($p < 0.001$), although the SIRs for all second cancers and ovarian cancer in premenopausal women were borderline significantly elevated after the correction.

[b] Central nervous system.

borderline significantly elevated risk for endometrial cancer were seen among women with premenopausal breast cancer. In postmenopausal women, the SIRs for cancers of the reproductive organs were below unity, the risk for cervical cancer being significantly reduced. A significantly increased risk for cancer of the gall-bladder and biliary tract was found in postmenopausal women and borderline significantly increased risks for rectal cancer were seen in both pre- and postmenopausal women.

We found overall significantly elevated risks in age groups <40 years and 50–54 years among women with premenopausal breast cancer; among postmenopausal women, we found no overall excess risk at or above age 50 years (Table 4). Premenopausal women who were under 40 years and those aged 40–44 years at the time of breast cancer diagnosis had elevated risks for ovarian cancer, with SIRs of 2.1 (95% CI, 0.6–5.3) and 2.3 (95% CI, 1.1–4.2), respectively. Premenopausal women with breast cancer at the age of 50–54 years were also at increased risk for ovarian and endometrial cancers, whereas postmenopausal women in the same age group had a markedly reduced risk for endometrial cancer. The risk for endometrial cancer was also significantly increased in premenopausal women diagnosed with breast cancer in their late 50s.

With respect to histological subtypes of breast cancer, premenopausal women with tubular carcinoma had the highest risk for endometrial cancer, although this finding is based on only four cases (Table 5). Of these women, three had receptor-positive breast cancer and one had unknown receptor status (data not shown). The risk for cancer of the ovaries was markedly elevated among premenopausal women with medullary carcinoma, and less so among those with lobular carcinoma. Most of these cases were of unknown receptor status, but we found a significantly elevated risk for ovarian cancer in women with premenopausal receptor-negative breast cancer, independent of histological type (eight cases; SIR, 4.8; 95% CI, 2.1–9.4) (data not shown). Premenopausal women with medullary breast cancer had a significantly elevated risk for cancer of the bladder (three cases; SIR, 12.0; 95% CI, 2.4–35.0) (data not shown).

Among premenopausal women in programmes 77 and 82 combined, the SIRs for all second cancers were significantly increased during latency periods 5–9 years (59 cases; SIR, 1.4; 95% CI, 1.1–1.8) and 10+ years (204 cases; SIR, 1.2; 95% CI, 1.0–1.3). No elevated SIRs were seen for latency period 5–9 years (14 cases; SIR, 0.9; 95% CI, 0.5–1.5) and latency period 10+ years (19 cases; SIR, 1.0; 95% CI, 0.6–1.5) among those in programme 89 and among those in programmes 99, 01 and 04 combined (three cases; SIR, 1.2; 95% CI, 0.3–3.6) (data not shown).

When the Bonferroni correction was used some of the SIR estimates remained significantly or borderline significantly elevated (see footnotes in Tables 3–5).

Table 4 – Observed numbers (Obs) and standardised incidence ratios (SIRs) of all second primary cancers and cancers at selected sites in pre- and postmenopausal 1-year survivors with a first invasive breast cancer who underwent surgery alone during 1977–2006 in Denmark stratified by age at breast cancer diagnosis.

Age at breast cancer (years)	Menopausal status at breast cancer diagnosis																	
	Premenopausal									Postmenopausal								
	All[a]			Corpus uteri			Ovary			All[a]			Corpus uteri			Ovary		
	Obs	SIR	95% CI	Obs	SIR	95% CI	Obs	SIR	95%CI	Obs	SIR	95%CI	Obs	SIR	95%CI	Obs	SIR	95%CI
<40	37	1.6	1.1–2.2	2	1.2	0.1–4.3	4	2.1	0.6–5.3	0	–	–	0	–	–	0	–	–
40–44	62	1.2	0.9–1.5	5	1.1	0.4–2.6	10	2.3	1.1–4.2	2	2.6	0.3–9.2	0	–	–	0	–	–
45–49	107	1.0	0.8–1.2	10	1.1	0.5–2.0	10	1.2	0.6–2.3	16	1.8	1.0–2.9	1	1.3	0.0–7.0	2	2.8	0.3–10.2
50–54	124	1.4[b]	1.2–1.7	14	1.8	1.0–3.0	14	2.3	1.2–3.8	66	0.9	0.7–1.1	2	0.3	0.0–1.1	7	1.3	0.5–2.7
55–59	13	0.8	0.4–1.4	5	3.5	1.1–8.3	0	–	–	197	1.0	0.9–1.1	14	0.8	0.4–1.4	14	1.1	0.6–1.8
>60	0	–	–	0	–	–	0	–	–	662	0.8	0.7–0.8	45	0.9	0.7–1.3	24	0.7	0.4–1.0

[a] All second primary cancers except second breast cancer.
[b] SIR of statistical significance after the Bonferroni correction ($p < 0.002$).

Table 5 – Observed numbers (Obs) and standardised incidence ratios (SIRs) of all second primary cancers and cancers at selected sites in pre- and postmenopausal 1-year survivors with a first invasive breast cancer who underwent surgery alone during 1977–2006 in Denmark stratified by histological subtype of breast cancer.

Histological type	Menopausal status at breast cancer diagnosis																	
	Premenopausal									Postmenopausal								
	All[a]			Corpus uteri			Ovary			All[a]			Corpus uteri			Ovary		
	Obs	SIR	95% CI	Obs	SIR	95% CI	Obs	SIR	95% CI	Obs	SIR	95% CI	Obs	SIR	95% CI	Obs	SIR	95% CI
Ductal	252	1.1	1.0–1.3	26	1.4	0.9–2.0	24	1.4	0.9–2.1	733	1.0	0.9–1.1	46	0.8	0.6–1.1	41	1.0	0.7–1.3
Lobular	44	1.5[b]	1.1–2.1	5	2.0	0.7–4.8	6	2.8	1.0–6.0	112	1.1	0.9–1.3	5	0.6	0.2–1.5	2	0.3	0.0–1.2
Medullary	16	2.4[b]	1.3–3.8	0	–	–	7	13.3[c]	5.3–27.5	17	0.9	0.5–1.5	1	0.7	0.0–3.8	0	–	–
Tubular	8	0.7	0.3–1.4	4	4.2	1.1–10.7	0	–	–	18	0.8	0.5–1.3	2	1.2	0.1–4.4	1	0.8	0.0–4.4
Other and unknown	23	1.5	0.9–2.2	1	0.8	0.0–4.2	1	0.9	0.0–4.7	63	0.9	0.7–1.1	8	1.5	0.7–3.0	3	0.7	0.2–2.2

[a] All second primary cancers except second breast cancer.
[b] SIR of borderline significance after the Bonferroni correction ($p < 0.002$).
[c] SIR of statistical significance after the Bonferroni correction ($p < 0.002$).

4. Discussion

In our study, women with a first primary breast cancer before menopause treated by surgery alone had an 18% higher risk for a second primary non-breast cancer than the general female population of Denmark. Women with breast cancer after menopause who underwent surgery alone had no overall excess risk for a second cancer.

To our knowledge, no more than three previous studies have addressed the risk for second cancer separately among women who underwent surgery alone in comparison with the general female population.[9,10,12] Two of these studies reported SIRs for only a few selected cancer sites;[9,12] the third study, by Rubino et al., of 1115 patients with breast cancer diagnosed at the Institut Gustave Roussy in France in 1954–1984, found no overall excess risk for a second cancer (SIR, 1.0; 95% CI, 0.7–1.4).[10] These authors did not estimate the overall risk of women treated by surgery alone by menopausal status; however, when we combine our results for pre- and postmenopausal women, our overall risk for a second cancer is similar (SIR, 1.01) to that reported by Rubino et al.

Our results show that both age and menopausal status at breast cancer diagnosis are important predictors of a second cancer. For instance, the overall risks of women in whom breast cancer was diagnosed when they were in their early 50s differed somewhat after stratification by menopausal status. Significantly elevated risks for endometrial and ovarian cancers were seen in women who were still premenopausal in their 50s. This finding is in accordance with the results of previous studies, which consistently showed that a relatively late menopause increases the risks for endometrial[21,22] and ovarian cancer.[23]

Previous studies not restricted to 'surgery only' patients show a decreasing trend in the risk for a second cancer with increasing age at breast cancer diagnosis.[5,8] We also found that the risk was most pronounced among the youngest patients less than 40 years, although no clear trend was seen with increasing age at breast cancer diagnosis. Germline mutations in the tumour suppressor genes *BRCA1* and *BRCA2* predispose to both breast and ovarian cancer,[24] and a particularly strong decreasing trend with increasing age at breast cancer diagnosis has been seen for ovarian cancer.[3,5,7,8] Such a trend was not seen in our study, perhaps because *BRCA1* mutations are more common in women with oestrogen receptor-negative or high-grade tumours[25,26] and would therefore tend to be less prevalent among the low-risk patients (as defined by DBCG) included in our study.

We found that premenopausal women with medullary breast cancer and premenopausal women with negative-receptor status had particularly high risks for cancer of the ovaries. This is in agreement with the fact that medullary histology is more frequent in *BRCA1*-associated breast cancer[26,27] and that most of *BRCA1*-associated breast cancers are negative for oestrogen receptors.[25,26] To our knowledge, no previous study has investigated the risk for a second cancer in women with rare histological subtypes of breast cancer, such as medullary and tubular breast carcinomas, and our study is the first to report an excess of endometrial cancer among women with tubular breast carcinomas.

An elevated risk for cancer of the gallbladder and biliary tract was seen in postmenopausal women with breast cancer in our study. Obesity predisposing to both gallbladder[28] and postmenopausal breast cancer[29] may explain this finding. Since obesity as well as hormonal factors is associated with both endometrial and postmenopausal breast cancer,[21,29] it is surprising that we found no excess of endometrial cancer among the women with postmenopausal breast cancer in our study.

A markedly reduced risk was seen for cervical cancer in these women, which could be explained by increased screening in comparison with the general female population, thus detecting cervical lesions before they become invasive. Moreover, the decreased risk could be related to differences in social class related lifestyle factors, since breast cancer is associated with high socioeconomic position[29] while cervical cancer is associated with low socioeconomic position.[30]

The strengths of this study include the population-based nature of our cohort and the use of register data collected independently of our hypotheses. The detailed information on treatment in the DBCG database enabled us to identify patients who underwent surgery alone. In addition, within the clinical monitoring by DBCG up to 10 years following the breast cancer diagnosis, we censored study subjects on date of recurrence or second breast cancer, so treatment for these events did not affect the results.

As our focus was on the absence of radiotherapy and systemic treatment, we included patients defined as low-risk patients by the DBCG, although their definition has changed over time. The elevated risks for all second cancers during latencies above 5 years found among premenopausal breast cancer patients in DBCG programmes 77 and 82 combined, but not among those in programme 89, were, in our opinion, unlikely to be explained neither by the change in risk criteria nor by a moderate change in the frequency of breast conserving surgery in programme 89. In addition, the SIR estimates for premenopausal patients in programme 89 were based on a limited number of observed cases, thus making it difficult to detect an excess. However, we cannot totally reject that changes in patient's mixture during the study period may have influenced the findings. As described previously, not all breast cancer patients are included in the DBCG programmes, but in our opinion these exclusions are likely to have affected our results only to a minor degree. The relatively high number of subgroup analyses may have led to chance findings, and the Bonferroni correction was used to address this problem. Only few associations remained statistically significant after the correction, but it should be noticed that the method has been criticised for increasing the probability of false negative findings.[31]

In conclusion, this large population-based study of breast cancer patients treated by surgery alone suggests that an excess risk for second cancers, related to non-treatment factors such as a shared genetic predisposition or common risk factors, occurs primarily in women with premenopausal breast cancer.

Conflict of interest statement

None declared.

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