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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.