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Outcomes of surveillance for contralateral breast cancer in patients less than age 60 at the time of initial diagnosis

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ABSTRACT

Background

After an initial diagnosis of breast cancer, the risk of contralateral breast cancer is approximately 0.5% per year. Annual mammography is recommended to identify local recurrences and contralateral new primaries. Because the sensitivity of mammography tends to be lower in younger women, we conducted a retrospective review of the method of detection and pathologic stage of metachronous contralateral primary breast cancers according to age at diagnosis in a cohort of breast cancer patients.

Methods

The Henrietta Banting Database contains information on cases of breast cancer diagnosed at Women's College Hospital from 1987 to 2004. From among 1992 women in the database, 71 patients were identified who were initially diagnosed before age 60 and who subsequently developed a contralateral breast cancer. Medical records were obtained for 53 of the 71 patients.

Results

Of the 53 contralateral cancers, 33 (62%) were detected by mammography, including 4 in 16 patients (25%) diagnosed before age 50 and 29 in 37 patients (78%) diagnosed at age 50 or older ($p \leq 0.001$).

Conclusions

Mammography has poor sensitivity for the surveillance of contralateral breast cancer in early-onset breast cancer patients. Other imaging modalities should be evaluated in this setting.

KEY WORDS

Breast cancer, surveillance, mammography, detection, contralateral cancer

1. INTRODUCTION

Breast cancer survivors face a higher risk of developing a contralateral tumour than do women who have never had breast cancer. The risk is estimated to be approximately 0.5% per year, and it does not depend on age at diagnosis or time since diagnosis [1]. Metachronous breast cancer has been shown to have a negative impact on long-term overall survival [2]. With advances in treatment since the early 1990s, including targeted therapy, survival for women with localized breast cancer has dramatically increased. Thus, the need for effective surveillance to diagnose contralateral cancers at a curable stage is of increasing concern.

Current guidelines recommend that after completion of therapy for a primary breast cancer, women should undergo annual surveillance mammography to detect metachronous contralateral cancers [3]. However, in breast cancer screening trials and programs for the general population, the sensitivity of mammography is lower for women in their 40s than for women more than 50 years of age [4]; it would therefore follow that, for surveillance, mammography may be less effective in breast cancer survivors younger than 50 years of age than in older women.

There are several explanations for the reduced sensitivity of screening mammography in younger women. On average, compared with older women, young women have higher breast density, resulting in intrinsically lower mammography sensitivity [5,6]. Also, age and breast cancer growth rate show an inverse relationship [7–10], resulting in a higher interval cancer rate independent of breast density. Assuming that early detection of new breast tumours confers a survival advantage [11], it is important to know whether

contralateral tumours are actually being detected at an early stage when conventional screening guidelines are followed.

We conducted a retrospective review of the method of detection and pathologic stage of metachronous contralateral primary breast cancers in an inception cohort of breast cancer patients.

2. METHODS

The Henrietta Banting Breast Center (HBBC) maintains a database that contains baseline and follow-up information on all new cases of operable invasive breast cancer diagnosed at Women's College Hospital for the period 1987–2004 [12]. The HBBC database records data on clinical presentation, treatment, and outcome for women who received their primary surgical treatment for breast cancer at Women's College Hospital. Patients were originally referred from family physicians and other physicians from the surrounding medical community to 1 of 5 teaching surgeons at HBBC. Follow-up is maintained by the database coordinator through review of clinical charts and direct telephone contact with patients [13].

From among the 1992 women in the database, we identified 71 patients who were diagnosed with an initial cancer before the age of 60 and who subsequently developed a contralateral breast cancer diagnosed in the absence of distant metastatic disease. Because details of the mode of detection are not routinely recorded in the database, it was necessary to retrieve the original medical records for these patients. The medical records for 53 of the 71 patients (75%) were obtained. The records were reviewed to obtain data on detection method and pathology of the second tumours (pathology details of the first tumours are recorded in the HBBC database). Estrogen receptor (ER) and progesterone receptor (PR) statuses were determined by reviewing each patient's pathology records. Per the standard of care at the time of time of diagnosis, ER and PR statuses were determined either by biochemical assay or immunohistochemical study. Because 18 patients were treated elsewhere for the second tumour, data on second cancers in those patients could not successfully be obtained. Pathology reports on second tumours treated elsewhere are not routinely stored in the HBBC database.

For each contralateral tumour, the method of detection was recorded as either self-detection, physician examination, or mammography. One cancer was detected at reduction mammoplasty. The method of detection of the contralateral cancer was compared between age groups, using a *t*-test for statistical significance.

3. RESULTS

Details of the HBBC database have previously been described [12]. Table I contains a description of the age distribution of the 53 patients in the study and of their first primary cancers. Table II presents the methods of detection of the contralateral breast cancers by age group. Mammography was the most common method of diagnosis. Overall, 62% ($n = 33$) of the 53 second primary breast cancers were detected in a surveillance mammogram. However, the proportion detected by mammography varied with age at diagnosis. Of the contralateral tumours, only 25% were diagnosed by mammography in women under the age of 50, compared with 78% in women 50 years of age and older ($p \leq 0.001$). Self-detection by the patient was the second most common method of diagnosis. Two tumours were detected by the clinician during routine follow-up, and one diagnosis was made from a pathology specimen obtained during reduction mammoplasty. Of the 12 patients under 50 years of age whose cancer was detected by a method other than mammography, a negative screening mammogram had been documented in 75% within the 15 months preceding diagnosis. The other patients had likely undergone mammography, but the reports were unobtainable on chart review.

Table III shows the characteristics of the contralateral tumours according to age group. In all

TABLE I Age distribution and characteristics of initial breast tumours in the study population

Characteristic	*Value*
Age (years)	
Mean	48.15
Range	34–60
Age groups [*n* (%)]	
31–40 Years	8 (15)
41–50 Years	22 (42)
51–60 Years	23 (43)
Pathologic T-stage [*n* (%)]	
Tis	0 (0)
T1	30 (57)
T2	19 (36)
T3	4 (8)
Nodal status [*n* (%)]	
Negative	31 (58)
Positive	21 (40)
Unknown	1 (2)
Hormone receptor status [*n* (%)]	
ER-positive	33 (62)
ER-negative	14 (26)
Borderline	3 (6)
Unknown	3 (6)

ER = estrogen receptor.

TABLE II Method of detection of contralateral breast tumours in the study population

Method of detection	*Age group [mean age (*n *patients)] at diagnosis, years*			
	Overall [54.94 (n=53)]	*<50 [45.0 (n=16)]*	*50–59 [55.63 (n=22)]*	*>60 [64.53 (n=15)]*
Mammography [*n* (%)]	33 (62)	4 (25)	17 (77)	12 (80)
Self-detection [*n* (%)]	17 (32)	11 (69)	3 (14)	3 (20)
Physician [*n* (%)]	2 (4)	1 (6)	1 (5)	0 (0)
Other [*n* (%)]	1 (2)	0 (0)	1 (5)	0 (0)

age groups, most of the detected tumours were early-stage, with 65% (n = 11) of the tumours in patients younger than 50 and 70% (n = 26) in older patients being T1 (or noninvasive). However, a higher proportion of tumours in the younger group were advanced, with 25% (n = 4) of the tumours in the younger group and 8% (n = 3) in the older group being T3 or higher (p = 0.18). One patient developed inflammatory carcinoma of the breast 1 year after her initial breast cancer was diagnosed; she was 43 at the time of the second diagnosis. A mammogram obtained after she had completed therapy for her initial tumour was negative. For 25% (n = 11) of the women with invasive cancers, axillary node status was unknown, but in 45% (n = 5) of those patients, the primary tumour was smaller than 1 cm. For 2 of the patients, the pathology reports were unobtainable.

For the 10 patients under 50 years of age whose first tumour was self-detected, 7 (70%) also self-detected their second cancer. In the 5 patients under 50 years of age whose first tumours were detected by screening mammography, only 2 patients (40%) had their contralateral tumours detected by mammography as well. Of the 13 patients older than 50 whose initial tumour was diagnosed by screening mammography, 12 (92%) had their second cancer also detected by surveillance mammogram. For the 20 patients older than 50 whose first tumour was self-detected, 14 (70%) had their second tumours detected by mammography.

4. DISCUSSION

In our study, only 25% of metachronous contralateral breast cancers in breast cancer patients less than 50 years of age were detected by an annual surveillance mammogram. Previous studies have reported that 50%–72% of ipsilateral recurrences [14–17] and 37%–80% of contralateral new primaries [17–21] are mammographically-detected. Two studies also reported that the sensitivity of surveillance mammography was lower

TABLE III Pathology of contralateral tumours by age group

Variable	*Age group at diagnosis (years)*			
	Overall	*<50*	*50–59*	*>60*
All cancers (*n*)	53	16	22	15
Size [*n* (%)]				
In situ	9 (17)	3 (19)	6 (27)	0 (0)
T1	29 (55)	8 (50)	9 (41)	11 (73)
T2	6 (11)	1 (6)	5 (23)	1 (7)
T3+	7 (13)	4 (25)	1 (5)	2 (13)
Unknown T stage	2 (4)	0 (0)	1 (5)	1 (7)
Invasive tumours (*n*)	44	13	16	15
Nodal status [*n* (%)]				
Negative	22 (50)	8 (62)	7 (44)	7 (26)
Positive	11 (25)	4 (31)	5 (30)	2 (13)
Unknown	11 (25)	1 (8)	4 (25)	6 (40)
Grade [*n* (%)]				
1	6 (11)	1 (6)	3 (14)	2 (13)
2	17 (32)	5 (31)	6 (27)	6 (40)
3	19(36)	8 (50)	9 (41)	2 (13)
Unknown	11 (21)	2 (13)	4 (18)	5 (33)
Hormone receptor status [*n* (%)]				
ER+ or PR+, or both	34 (64)	9 (56)	15 (68)	10 (67)
ER– and PR–	3 (6)	2 (13)	1 (5)	0 (0)
Unknown	16 (30)	5 (31)	6 (27)	5 (33)

ER = estrogen receptor; PR = progesterone receptor.

in young women with a past history of breast cancer than in their older counterparts. In a study of 65 patients who developed contralateral cancers, 50% of 44 cancers in patients older than 50 were detected by mammography, but only 9.5% of 21 cancers in patients 49 years of age and younger were detected by mammography [19]. A second study also found that only 17% of second primary tumours in patients under 40 were diagnosed mammographically compared with 59% in patients between the ages of 55 and 60 [21].

In the present study, the breast cancers diagnosed in younger women were, on average, at a more advanced stage than the tumours detected in older women. A review of mammography screening studies in the general population showed a direct correlation between the ability of mammography to lower the stage distribution of cancers and a reduction in breast cancer mortality [22].

The relatively poor performance of surveillance mammography in younger women is likely attributable, at least in part, to the greater breast density and more rapid growth of tumours in younger women than in older women. In our study, 50% of women in their 40s and 13% of women older than 60 had

grade 3 tumours. However, an additional possible explanation is that some of the second primary tumours may have been attributable to hereditary causes. Our study did not differentiate between women with or without *BRCA* mutations. Cancers in premenopausal women are more likely to be associated with specific mutations such as *BRCA1* and *BRCA2*. In particular, cancers attributable to *BRCA1* have been shown less commonly to involve ductal carcinoma *in situ,* and thus to have fewer microcalcifications that aid in mammographic detectability. Also, the rounded margins of *BRCA1*-related cancers tend to be less amenable to detection than the irregular infiltrating margins of "conventional" tumours [23]. However, fewer than 10% of breast cancers in women under the age of 40 are expected to carry a mutation in *BRCA1* [24].

We also found that many of the tumours diagnosed in the young women in our study were node-positive, and almost one third were locally advanced at the time of diagnosis. Those findings might result from a lack of effective early detection, but might also reflect the more aggressive course of disease in younger compared with older patients with breast cancer.

It appears from our data—and from previous studies—that conventional-film screening mammography is a poor tool for surveillance for contralateral breast cancer in women under 50 years of age. Other possibilities for surveillance of the contralateral breast include digital mammography, ultrasonography, and magnetic resonance imaging (MRI). In a large multicentre study involving 42,760 patients, digital mammography was found to be significantly more sensitive than conventional-film mammography in detecting tumours in patients younger than 50, without a loss of specificity. However, 32% of cancers in women younger than 50 were still missed by digital mammography [25]. Breast ultrasonography detects many mammographically occult cancers in young women, but is associated with a high false-positive rate [26].

In both the diagnostic and high-risk screening settings, MRI has consistently been found to be more sensitive than mammography or ultrasonography. In studies in which women with a recent diagnosis of breast cancer who had a normal contralateral physical examination and mammogram underwent perioperative MRI, contralateral cancers were detected in 3%–4% of patients [27,28]. However, few data are available on surveillance for contralateral breast cancer using MRI in the years after the initial diagnosis. Because MRI is less specific than mammography and much more expensive, it should not be adopted for use in any population without properly conducted studies. Whether it would be a cost-effective tool for the surveillance of young breast cancer survivors and perhaps somewhat older survivors with dense breasts could be an important area for future research. In a multi-institutional survey in Toronto, we found that 58% of breast cancer patients younger than 60 would be willing to participate in a randomized controlled trial of annual digital mammography with or without MRI [29].

5. CONCLUSIONS

Our population-based study found that a high proportion of clinically-detected contralateral breast cancers in young women were associated with a negative surveillance mammogram in the 15 months before the contralateral cancer diagnosis. The current recommendation for annual surveillance mammography for young women with a history of breast cancer may not be adequate for finding contralateral tumours at an early stage. Studies to determine the best surveillance strategies in young women are warranted.

6. CONFLICT OF INTEREST DISCLOSURES

The authors have no financial conflicts of interests to disclose.

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