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Original article

Towards evidence-based follow-up intervals for breast cancer survivors: Estimates of the preclinical detectable phase of contralateral second breast cancer

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ABSTRACT

Purpose: Follow-up schemes in breast cancer survivors are predominantly consensus-based. To determine evidence-based follow-up intervals, estimates of sensitivity of the screening test(s) and duration of the preclinical detectable phase (PCDP) are key. We estimated the sensitivity and the duration of the PCDP of clinical breast examination (CBE) and mammography for the detection of contralateral second breast cancers (CBC) in breast cancer survivors.

Methods: Women with a CBC (N = 589) diagnosed in Florence between 1980 and 2005 were included. Test sensitivity and the duration of PCDP were estimated using a simple exponential model of PCDP duration. Analyses were stratified by follow-up period (0–5 vs. >5 years after primary diagnosis) and age at CBC diagnosis (<50 vs. ≥50 years).

Results: For CBE, test sensitivity was 55% and the duration of the PCDP 16 months. Mammography sensitivity was 91% and duration of the PCDP 35 months. Stratified analyses showed a higher test sensitivity for CBE for women aged <50 (70% vs. 51%). No difference in the duration of PCDP of CBE was found. For mammography, test sensitivity and the duration of the PCDP were higher for women with longer follow-up and in older women.

Conclusions: Poor test sensitivity for CBE with a shorter duration of the PCDP compared with mammography were observed. Mammography had high test sensitivity and the potential to detect CBCs early. The estimated duration of the PCDP (35 months) was considerably longer than the recommended follow-up interval (12 months). Future studies are needed to determine whether a longer follow-up interval is appropriate.

1. Introduction

Breast cancer is the most common cancer in women worldwide with nearly 1.7 million new cases diagnosed in 2012 [1]. Increasing breast cancer incidence and expanding screening practice together with improved treatment modalities and survival rates have contributed to growing numbers of breast cancer survivors. For these breast cancer survivors, follow-up by means of routinely providing clinical breast examination (CBE) and mammography is standard medical practice and recommended in contemporary follow-up guidelines [2]. The primary objective of follow-up is the early detection of locoregional recurrences and second primary cancers (ipsilateral and contralateral). Other aims of cancer follow-

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up are providing psychosocial care and monitoring (late) side-effects of primary treatment.

In contrast to primary breast cancer screening, current breast cancer follow-up schemes are still predominantly consensus-rather than evidence-based. Although several studies have shown that early detection of ipsilateral breast recurrences (IBR) and contralateral second breast cancers (CBC) improves survival [3], the optimal follow-up schedule in terms of frequency has never been defined. Since all patients treated for breast cancer with curative intent are offered routine follow-up but not all patients will face IBR or CBC, this raises the question whether overall a favourable balance between benefits and harms of follow-up is achieved. Harms may be caused by an advanced diagnosis of untreatable or incurable recurrences, psychosocial consequences of the routine test itself or clinical or psychological sequelae of false negative and false positive test findings. Early detection of incurable recurrences may decrease patients' quality of life due to the advance knowledge of the recurrence and longer treatment period, without improving longevity. Tests with a low sensitivity result in a large proportion of false negative findings, wrongly reassuring the patient and delaying recurrence detection. Low specificity, however, results in false alarms, causing emotional distress and unnecessary diagnostic testing. The diagnostic tests themselves can be unpleasant and associated with serious side-effects and thus may negatively affect quality of life.

In primary breast cancer screening, the screening interval is evidence-based and related to the sensitivity of the screening test and the duration of the preclinical detectable phase (PCDP) [4]. The shorter the PCDP, the more quickly cancers arrive at the symptomatic phase. As a consequence, the shorter the screening interval has to be in order to achieve a worthwhile programme sensitivity (i.e. a high proportion of cancers which are detected by screening) and mortality reduction. The same principle holds for breast cancer follow-up for the early detection of CBC. We envision that the methodology used to determine the mammography interval in breast cancer screening can also be used to determine the optimal CBE and mammography intervals in breast cancer follow-up. IBR is different, since it is difficult to distinguish ipsilateral recurrences from ipsilateral second primary tumours which have a different biology and possibly a different duration of PCDP, while for CBCs the tumour population is more likely to be relatively homogeneous. Moreover, the incidence of CBCs resembles the incidence of primary tumours and therefore meets the requirements for using traditional exponential models for the PCDP. We therefore focus on CBC in this paper.

In this study, we estimated the sensitivity and duration of PCDP of clinical breast examination and mammography for the detection of contralateral second breast cancers to provide guidance on the optimal follow-up interval for breast cancer survivors.

2. Methods

2.1. Patients

A retrospective cohort study was performed based on data from the clinical and pathology archives of the *Centro per lo Studio e la Prevenzione Oncologia* (CSPO) in Florence, Italy, from January 1980 to December 2005. The archives were searched for women with two breast cancer histology episodes, separated by at least 6 months. Eligibility was verified by reviewing medical and mammography records. In total 1044 histology-verified second breast cancers, including 589 CBCs, were identified from 24,278 breast cancer histology records [5,6]. The following definition for women with a CBC was used: women who had a primary breast cancer and subsequently developed a second cancer in the opposite breast. Women with metastatic cancer at diagnosis of the second breast cancer, representing a very small proportion of women, were not considered for this study as histological verification is inconsistently available in these cases. Women presenting primarily with nodal metastases or chest wall recurrences (following mastectomy for the primary breast cancer) were also excluded [6].

At CSPO, Florence's main breast screening and diagnostic centre, all women with a history of breast cancer were offered breast cancer follow-up. The following follow-up scheme was recommended at CSPO throughout the time frame of the study: CBE (6-monthly) and annual mammography (analogue) for the initial 5 years in women treated with breast conservation, thereafter annual CBE with annual or biennial mammography; annual CBE and annual or biennial mammography in women treated with mastectomy.

For 589 women with a CBC, the data retrieved from clinical records included date of birth; date of diagnosis, histology and pathological T and N category of the primary breast cancer; date of diagnosis, side, histology and pathological T and N category of the CBC; presence or absence of symptoms (lump or focal mass, nipple discharge, skin change and axially mass) at diagnosis of CBC; detection by CBE and/or mammography; surgical management; and date of last follow-up visit. No data were collected on adjuvant treatment.

2.2. Data analysis

We estimated test sensitivity and the duration of the PCDP of CBE and mammography separately using Launoy's formula for the relationship between programme sensitivity and test sensitivity [7]. We did not have data on the exact dates of follow-up visits. Therefore, we used information on whether a CBC was symptomatic or asymptomatic when detected at routine follow-up and whether the cancer was detected by CBE, mammography or both. The mode of detection (CBE, mammography or both) was recorded for only 497 out of the 589 CBCs.

Test sensitivity, programme sensitivity and the duration of the PCDP (or its inverse, the rate of transition from asymptomatic to symptomatic disease) are interrelated, so if we have estimates of two of the parameters, we can use this relationship to subsequently estimate the third. Given the data, there is no perfect way to estimate all three parameters. We first estimated the two sensitivity parameters and used the relationship (as expressed in Launoy's formula) to estimate the PCDP. The test sensitivity estimates the probability of detecting asymptomatic disease if it is present. Thus, we estimated the test sensitivity for a given modality (mammography or CBE) as the number of CBCs detected by that modality (numerator) divided by the total number of CBCs detected by one or both modalities (denominator); see supplementary Table S1. The rationale for the denominator is that we restrict the CBCs to those with complete known test results.

The programme sensitivity estimates the proportion of all cases in women attending a programme (asymptomatic and symptomatic) which is detected by the modality (asymptomatic), corresponding as closely as we could to programme sensitivity in a population screening programme. Thus, we used the same numerator for the estimation of the programme sensitivity for each modality separately. The denominator was 556 which consisted of the 497 previously mentioned CBCs plus 59 symptomatic CBCs with incomplete results by the modalities; see supplementary Table S1. We did not include 25 asymptomatic cases with both mammography and CBE results unknown from the programme sensitivity calculation; see supplementary Table S1. Moreover, there were 8 asymptomatic cases, detected by CBE but with unknown mammographic status. If these 8 cases were included in the

numerator and denominator of the programme sensitivity for mammography, this might overestimate the programme sensitivity, since some may have been undetected by mammography. On the other hand, if they were included in the denominator only, this might underestimate the programme sensitivity since some of them may have been detected by mammography, but we do not have the information. We therefore also excluded these 8 cases from the programme sensitivity calculation. Examples of calculation of test and program sensitivity can be found in supplementary Table S1. Moreover, our method to estimate the duration of the PCDP is depicted in supplement 2.

We performed stratified analyses to investigate differences in test sensitivity and duration of the PCDP by time between the primary breast cancer diagnosis and the CBC diagnosis, and the age at CBC diagnosis. Some breast cancer follow-up schemes include less frequent follow-up tests starting 5 years after the primary breast cancer, because incidence of second primaries is lower after five years and endocrine treatment is usually finished. From studies performed in the context of breast cancer screening we know that the duration of the PCDP is dependent on the age at diagnosis [8].We therefore divided all CBCs into those occurring 0–5 years and >5 years after diagnosis of the primary breast cancer and age at CBC diagnosis, <50 years versus ≥50 years.

3. Results

Two-thirds of the CBCs were diagnosed in the absence of clinical symptoms. A summary of the characteristics of symptomatically and asymptomatically detected CBCs is given in Table 1. The median time between primary and second breast cancer was 59 months for symptomatic CBCs and 75 months for asymptomatic CBCs. Asymptomatic CBCs were mostly detected by mammography alone (57%), while symptomatic CBCs by both tests (58%). Asymptomatic CBCs were smaller and less likely to be node positive than symptomatic CBCs. Moreover, cases of ductal carcinoma in situ (DCIS) were more often detected without symptoms. For 16% of all the CBCs the mode of detection (CBE, mammography or both) was not recorded, especially for the symptomatic CBCs (25%).

The estimated sensitivity parameters and duration of the PCDP of BCE and mammography are given in Table 2. For all CBCs, mammography had a test sensitivity of 91%, which was higher than the test sensitivity of CBE of 55%. Programme sensitivity was 81% for mammography and 49% for CBE. The duration of the PCDP for mammography was almost 3 years (35 months) and 1.5 years for BCE (16 months).

The stratified analyses based on the time between primary breast cancer diagnosis and CBC diagnosis showed that test sensitivity was comparable between the two periods (0–5 year vs. >5 year) for both tests. For CBE, the duration of the PCDP was the same, while for mammography the duration of the PCDP was 1.5 times longer for the later period (43 vs. 26 months). Test sensitivities of mammography and CBE were comparable (76% vs. 70%) for women with an age at CBC diagnosis below 50. The duration of the PCDP of mammography was 18 months in the group of younger women and 40 months for the older women.

4. Discussion

In a well-characterised cohort of breast cancer survivors, we found that most CBCs were diagnosed in the absence of clinical symptoms (65%). Our analysis showed that CBE had a rather poor test sensitivity and a shorter duration of the PCDP compared with mammography. The estimated durations of the PCDP of CBE and mammography were 16 and 35 months respectively and thus considerably longer than the current follow-up interval of 12 months. The stratified analyses based on follow-up time and age at CBC diagnosis showed that the duration of the PCDP of mammography was higher for women with a longer follow-up time (>5 years) and for older women (≥50 years).

In the context of breast cancer, the duration of the PCDP has been estimated multiple times with methods ranging from simple to complex. The duration of PCDP of mammography we estimated

Table 1
Characteristics of symptomatic and asymptomatically detected contralateral second breast cancers in breast cancer survivors at CSPO.

	Patients with a contralateral second breast cancer (CBC) N = 589	
	Symptomatically detected N = 204 (34.6%)	Asymptomatically detected N = 385 (65.4%)
Median time between primary and second breast cancer (IQR), months	59 (17–101)	75 (31–119)
Median age at diagnosis of primary breast cancer (IQR), years	53 (44–62)	53 (44,5–61,5)
Median age at diagnosis of second breast cancer (IQR), years	60 (49–71)	63 (54–72)
Mode of detection (%)		
Only CBE positive	20 (10)	27 (7)
Only mammography positive	7 (3)	219 (57)
Both CBE and mammography positive	118 (58)	106 (28)
Only CBE positive (mammography not recorded)	9 (4)	8 (2)
Only mammography positive (CBE not recorded)	0	0
Both tests not recorded	50 (25)	24 (6)
Tumour size category (%)		
Tis	4 (2)	51 (13)
T1	110 (54)	287 (75)
T2+	67 (33)	38 (10)
Tx	23 (11)	9 (2)
Node status (%)		
Negative	100 (49)	230 (60)
Positive	59 (29)	57 (15)
Not examined	45 (22)	98 (25)
Histology (%)		
DCIS	4 (2)	50 (13)
Invasive ductal	103 (50)	160 (42)
Invasive lobular	44 (22)	71 (18)
Other types	53 (26)	104 (27)

CBE = clinical breast examination, DCIS = ductal carcinoma in situ.

Table 2
Estimation of test sensitivity, program sensitivity and the duration of preclinical detectable phase for clinical breast examination and mammography using Launoy's formula applied to data from breast cancer survivors at CSPO.

Test characteristics	All CBC	Time between primary breast cancer diagnosis and CBC diagnosis		Age at CBC diagnosis	
	All (n=556)	0-5 year (n=233)	> 5 year (n=264)	<50 years (n=87)	≥50 years (n=408)
Test sensitivity (%)*					
CBE	55	57	52	70	51
Mammography	91	86	94	76	94
Programme sensitivity (%)					
CBE	49	49	48	58	46
Mammography	81	75	87	62	85
Preclinical detectable phase (months)					
CBE	16	16	17	17	16
Mammography	35	26	43	18	40

CBE = clinical breast examination.

for CBCs (35 months) was comparable with PCDP estimates of primary breast cancers in the context of population screening, which range between 24 and 48 months [9–11]. Moreover, our estimate for test sensitivity of mammography, 91%, was comparable with estimates from breast cancer screening studies [9–11]. However, our estimate was high compared to estimated test sensitivities in the context of breast cancer follow-up [12,13]. This can potentially be explained by our method to estimate test sensitivity which was only based on positive test results [14]. Test sensitivity of CBE in the young age group (<50 year) was remarkably high (70%). This could not be explained by a high percentage of CBCs detected without clinical symptoms. Our hypothesis is that these result can be explained by the small size of the group and the missing data on the mode of detection. A limitation of this study is that for 16% of the CBCs the mode of detection (CBE, mammography or both) was unknown, meaning that our estimates for test sensitivity were based on data for 497 of the 589 CBCs (84%). In addition, our estimates of test sensitivity are likely to be overestimated, since the number of CBCs not detected by either follow-up test is unknown. To get an idea of the impact of this missing number of cancers on our estimates, we applied a capture-recapture exercise [15]. For CBE, test sensitivity decreased from 55 to 50% and the duration of the PCDP increased from 16 to 18 months after the capture-recapture exercise. Test sensitivity of mammography decreased from 91 to 83% and the duration of the PCDP increased from 35 to 40 months. As the percentage of missing information was 18% in the subgroup of women younger than 50, estimated test sensitivity of CBE dropped from 70 to 60%. Detailed information about the capture-recapture exercise and its results can be found in the supplement Tables S2 and S3.

Our estimates of the PCDP for CBE and mammography, 16 and 35 months respectively, are longer than the current follow-up interval (12 months). This suggests that current follow-up recommendations may be too intensive, potentially doing more harm than good. We investigated what would happen to the number of asymptomatically detected breast cancers when changing the follow-up interval to 24 months by applying Straatman's formula [16]. Straatman's method was developed to estimate the yield of detection of specific screening programs and previously applied to recurrences in laryngeal cancer [16–18]. Increasing the follow-up interval to 24 months led to a decrease in the proportion of asymptomatically detected CBCs from 71 to 53% for mammography meaning that less breast cancer will be detected at follow-up visits and presumably more in between visits. To judge whether this loss in benefit is acceptable, the exact effect of elongating the follow-up interval on the harms of breast cancer follow-up also need to be known. Less intensive follow-up will mean less opportunities to do harm, for example through unnecessary intervention from false-positives. Furthermore, our results of the stratified analyses based on follow-up time and age at CBC diagnosis showed that for women with a longer follow-up time and for older women the current follow-up interval might be too intensive. The current breast cancer follow-up scheme is one-size fits all within two groups defined by initial surgical treatment, but our results provide evidence in support of a more differentiated follow-up interval.

In this study we only focused on CBC, while breast cancer follow-up is also aimed at the early detection of IBR. In order to move to a more evidence-based follow-up interval for IBR, estimates for test sensitivity and the duration of the PCDP for these events are also needed. However, it is difficult to distinguish ipsilateral recurrences from ipsilateral second primary tumours which will possibly have a different duration of the PCDP, rendering the population of ipsilateral events highly heterogeneous. Moreover, previous research shows that the incidence of IBR is not constant but has a higher peak during the first two years after the primary tumour diagnosis [19]. The method used for CBC as well as other known methods used in the primary screening setting assume a constant underlying incidence and are therefore not appropriate. Therefore new analytic methods for IBR needs to be developed. This will be addressed in a future analysis.

Besides providing the evidence base for the optimal follow-up interval, as we did by estimating sensitivity and duration of the PCDP of CBE and mammography, there are other ways to improve detection from breast cancer follow-up such as the use of different or additional tests (e.g. ultrasound for women with dense breast patterns) and tailoring the follow-up scheme to groups at different levels of risk for recurrences (based on patient, tumour and treatment characteristics).

Thus, the next step towards evidence-based follow-up intervals is the performance of a modelling/simulation study using the previously gathered screening outcome data as well as data on incidence rates, treatment effectiveness for primary tumours, uptake of follow-up, length and quality of life and costs. The proposed modelling study can be used to model several follow-up intervals, the value of CBE or the introduction of new or additional tests, and to choose the follow-up schedule with the best benefit-harm balance. This is required to optimize current follow-up schedules and will lead towards more evidence-based follow-up.

In conclusion, test sensitivity for CBE was poor, but mammography had high test sensitivity and thus the potential to detect CBCs early. The estimated duration of the PCDP of CBE and mammography were both considerably longer than the current average follow-up interval of 12 months. Our study thus represents a first step towards optimizing evidence-based follow-up intervals, and can inform new research exploring whether a longer follow-up interval is appropriate.

Compliance with ethical standards

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent was obtained from all individual participants included in the study.

Conflicts of interest

Author Nehmat Houssami received funding from National Breast Cancer Foundation. The other authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.breast.2019.03.003.

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