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Diagnostic work-up of contralateral breast cancers has not improved over calendar period

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Abstract Women who have been treated for breast cancer are typically followed up with regular mammography and palpation, with the aim of detecting recurrences and contralateral breast cancer (CBC). This study aims to investigate if the diagnostic work-up of breast cancer patients has improved over the last 25 years and resulted in earlier diagnoses of CBC. Two population-based cohorts were used; all CBCs in Sweden 1976–2004 (*n*: 2932), and all CBCs in Stockholm, Sweden, 1976–2005 (*n*: 626), both cohorts with a maximum of 3 years between the two cancers. Synchronous CBC was defined as two cancers <3 months apart, the remainder was defined as metachronous CBC. We calculated the odds ratio of being diagnosed synchronously, relative to metachronously, using logistic regression, adjusting for whether the second cancer was detected through clinical work-up or not. The odds of synchronous CBC were significantly increased: 1.27 (95% CI, 1.13–1.42) per 5-year period, compared to metachronous, and was not affected by detection mode, but seemed to be explained by adjuvant therapy. The proportion of CBCs detected by clinical work-up did not increase over the study period, and the mean size of the second tumor remained constant. We found an increase in the proportion of synchronous CBCs compared to metachronous, over calendar period, a change that was not associated with clinical work-up, but with adjuvant therapy. This study gives no indications that any improvement in diagnostic work-up of CBC have occurred over the last 25 years.

Keywords Contralateral breast cancer · Diagnostic work-up · Time trends · Mammography

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Background

A primary breast cancer in the opposite breast, contralateral breast cancer (CBC), is diagnosed in 1–2.6% of all women with breast cancer within 3 months of their first diagnosis, this subtype is referred to as synchronous [1–4]. CBCs diagnosed more than 3 months after primary diagnosis has a stable incidence of 0.5% per year throughout life and are referred to as metachronous [5–8].

As we have previously shown, the incidence of synchronous CBC has increased considerably during the 1970s and 1980s, while the incidence of metachronous CBC has decreased steadily during the past 30 years [7]. Possibly, this pattern reflects a shift towards earlier diagnosis of existing tumors, making cancers formerly classified as metachronous to be diagnosed earlier and consequentially fall within the 3-month definition of synchronous CBCs. Such a shift could have occurred due to improved diagnostic work-up and more intense follow-up of women with breast cancer, e.g., the opposite breast is examined more

carefully and/or more often after a breast cancer diagnosis at present compared to earlier decades. An improvement like this could have several possible reasons: introduction of population-wide mammography screening [9, 10], improvements in mammographic technique [11], and implementation of nationwide follow-up routines of breast cancer patients. Also, it can not be excluded that increased public awareness of breast cancer has contributed. Another major change in the management of breast cancer during the last 25 years is the increased use of systemic adjuvant treatment [12–15], which may have decreased the incidence of metachronous CBC, thus further contributing to the observed incidence pattern.

The aim of the present study is to investigate to what extent improvements in the diagnostic work-up of breast cancer patients and change in use of systemic adjuvant therapy has contributed to an increasing proportion of synchronous CBCs.

Methods

Study population

The study population consists of women with CBC, we have restricted the group to patients with a maximum of 3 years between the diagnosis of their first and second breast cancer. The 3-year time limit was chosen arbitrarily, assuming that if the second cancer was diagnosed within 3 years, it was possible that it was present, though undetected, also at time of the first diagnosis. Patients with other malignant disease before or between the breast cancers were excluded. In one of the two cohorts used, where we also had the possibility to assess TNM stage, we did not include patients that had any of their cancers diagnosed in Stage IV. This was done to minimize the risk of the CBC being a metastasis of the first breast cancer, since it is not possible to assess from which cancer the metastasis originate from.

The two cohorts were assembled from population-based registers: the first cohort comprising all women with CBC in Sweden from 1976 to 2004, as ascertained from the nationwide and virtually complete Swedish Cancer Register [16, 17]. We retrieved information on dates of birth and cancer diagnosis for all patients. We refer to this as the national cohort.

We also established a second cohort, with more detailed information, consisting of all women with CBC diagnosed within 3 years between 1976 and 2005 in Stockholm county. The study participants in this cohort were selected from the Regional Oncological Center in Stockholm, where all new breast cancer cases in the Stockholm county health care region are recorded. The register, which covers a health care region of 1.9 million people, corresponding to approximately 20% of the Swedish population, provided us with information on date of birth, dates of diagnosis, stage and size of the tumors, as well as follow-up information for the patients. Below, we refer to this as the Stockholm cohort. For this cohort we also retrieved the medical records from the different oncology clinics where the patients were treated, and extracted information on detection mode of the two cancers, adjuvant therapy given for the first cancer and additional tumor characteristics. We also confirmed the diagnosis by reviewing all pathological reports.

For the purpose of calculating the proportion of breast cancer patients that develop CBC within 3 years of their first cancer, we used the Swedish Cancer Registry mentioned above, selecting all patients with primary breast cancer during 1976–2001 and excluding patients with other second malignancies except CBC. The reason for ending the study period at 2001 was to be able to calculate the proportion of women that develop CBC within 3 years, with full follow-up of all cases.

In the Stockholm cohort, mode of detection of the CBC was classified into four groups: (a) clinical work-up, which included CBCs detected through the follow-up program, by either mammography or palpation performed by health care personal, (b) self-palpation performed by the patient, (c) the national breast cancer screening program [10, 18], or (d) unspecified. The main comparison for our analysis: clinical work-up (a) versus the other modes (b–d), was expressed as binary variable 'clinical work-up' (yes/no). For further analysis, we also constructed an alternative binary variable 'clinical work-up including mammography screening' (yes/no), which contrasts modes a + c against b + d. Important to note in this context is that a woman with a primary breast cancer will not participate in the screening program for at least 5 years, during which she instead will be followed up by clinical mammography and breast palpation.

Adjuvant therapy can be given in a number of combinations, for the purpose of the analysis we have made three different comparisons. Firstly, we compared all CBCs patients that received any systemic adjuvant therapy for their first breast cancer (this includes hormone therapy, chemotherapy, or a combination of the two) with all who did not receive any such therapy (this group include patients who received radiotherapy only and those who did not receive any adjuvant therapy). The second comparison was made between patients who received chemotherapy (alone or in combination with any other adjuvant therapy) compared to those who did not. The third comparison was made between patients who received hormone therapy (alone or in combination with any other adjuvant therapy) and patients who did not receive hormone therapy.

Analysis

We used Spearman correlation to evaluate the possible correlation between latency time (time between cancers) and calendar period of first diagnosis and also between tumor size and calendar period of diagnosis. In the tumor size analysis we excluded all CBCs diagnosed on the same day, since in those 'first' and 'second' cancer can not be defined. Logistic regression was used to test for any trend over calendar period in the proportion of latency groups, the proportion of cancers diagnosed on the same day and the proportion of cancer diagnosed by clinical work-up.

To investigate the change in proportion of synchronous versus metachronous cancers over calendar period we used logistic regression and calculated the odds ratio, i.e., the odds that a cancer from the CBC-cohort was diagnosed synchronously as compared to metachronously. The logistic regression model included age at first diagnosis in 10-year groups, as a possible confounding factor. To asses the impact of each of the confounding factors on the changing proportion of synchronous/metachronous cancers, we sequentially adjusted our model for mode of detection of the second cancer and adjuvant therapy for the first cancer.

To investigate if the effect of calendar period on the timing of the CBC was different for younger/premenopausal women, compared to older/postmenopausal women we included an interaction term between calendar period and menopause status (defined as above/below 50 years of age, which is the mean age for menopause [19]). To allow for equal follow-up for all CBC patients we, in all analyses, excluded those that were diagnosed with their first cancer in the last 3 years of the follow-up period in both cohorts.

All data preparation and analysis was done using SAS statistical Package 9.1. This study was approved by the regional ethical review board at Karolinska Institutet, Stockholm, Sweden.

Findings

For the national cohort, we identified 2932 CBC patients diagnosed between 1976 and 2004. 58.1% were diagnosed synchronously (Table 1). The Stockholm cohort consisted originally of 691 CBC patients, 65 of whom were excluded either due to failing to fulfill inclusion criteria at medical records revision or that their medical record could not be found, thus leaving 626 cases in the cohort. 64.7% of the CBC patients were diagnosed synchronously and 68.6% had their second cancer diagnosed through clinical work-up, for 7% the mode of detection was unspecified.

In the national cohort, 3–4% of all breast cancer patients suffered a CBC within 3 years from their first diagnosis, this proportion remained constant over the calendar period. Among women with CBC, the proportion of synchronous cancers increased during the study period, constituting 49% of patients with their first cancer diagnosed in 1976–1978 and 67% of patients diagnosed at the end of the study period ($P < 0.0001$) (Fig. 1).

Table 1 Characteristics of the study cohorts

	National cohort	Stockholm cohort
Number of CBC patients	2932	626
Study period	1976–2004	1976–2005
Mean age at first breast cancer (years)	64.6	63.9
Median number of latency days	21	15.5
Synchronous CBC (%)	58.1	64.7
Number of CBC patients (%) in each period		
1976–1978	295 (10.1)	39 (6.2)
1979–1981	345 (11.8)	75 (12.0)
1982–1984	323 (11.0)	55 (8.8)
1985–1987	346 (11.8)	56 (8.8)
1988–1990	372 (12.7)	68 (10.9)
1991–1993	304 (10.4)	72 (11.5)
1994–1996	345 (11.8)	86 (13.7)
1997–1999	364 (12.4)	87 (13.9)
2000–2001	238 (8.1)	58 (9.3)
2002	–	31 (5.0)
CBC clinically detected (%)	–	68.6
First cancer treated with adjuvant therapy (%)	–	63.8

We found no significant correlation between latency time (number of days) and calendar period of first cancer ($P = 0.20$). Furthermore, the proportion of CBCs with both cancers diagnosed on the same day was similar through the period, ranging from 37% in 1976–1978 to 45% in 2000–2002 ($P = 0.41$).

For more in-depth analysis, we used the Stockholm cohort which, as expected, comprised approximately 20% of the national cohort. The risk of being diagnosed synchronously, as compared to metachronously, expressed as odds ratios, was statistically significantly associated with calendar period, OR = 1.27; 95% CI: 1.13–1.42, per 5-year period (Table 2). The association between calendar period and synchronous diagnosis persisted when we adjusted for mode of detection of the second cancer. However, adjusting for adjuvant therapy for the first cancer decreased the marked calendar period effect to a non-significant level (OR = 1.04; 95% CI: 0.90–1.20). We found furthermore that, when adjusting for chemotherapy and hormone therapy separately, the effect of calendar period

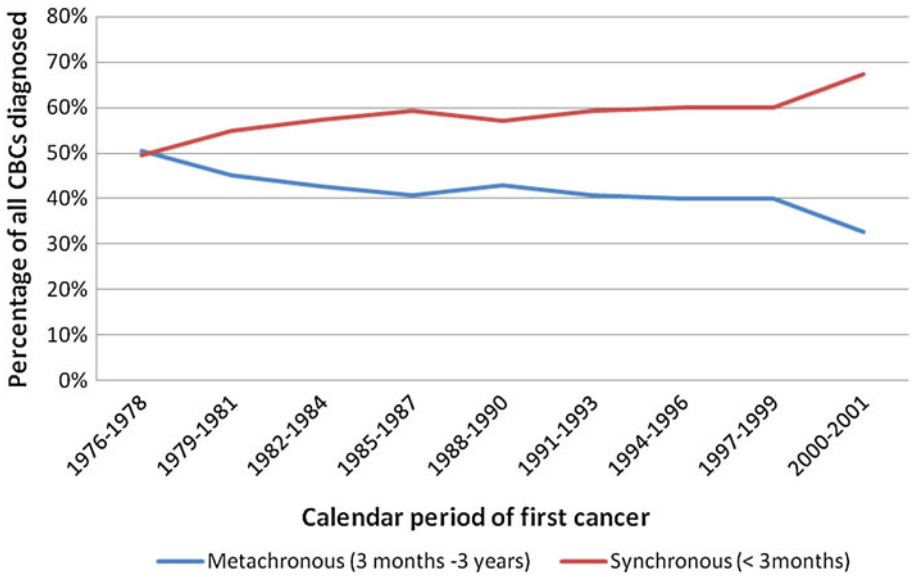

Fig. 1 Proportion of CBCs per latency category and calendar period of first diagnosis. Calculations for this graph use the national cohort. Note that these curves are each other's complements and add up to 100%

Table 2 Odds ratio estimate of being diagnosed synchronously, per 5-year period

	OR estimate	95% CI
OR	1.27	1.13–1.42
OR adjusted for mode of detection of second BC		
Clinical work-up	1.22	1.08–1.37
Clinical work-up including mammography screening	1.23	1.10–1.38
OR adjusted for adjuvant treatment of first BC	1.04	0.90–1.20
Hormone therapy vs. no hormone therapy	1.02	0.89–1.17
Chemotherapy vs. no chemotherapy	1.24	1.11–1.40

All odds ratios are adjusted for age at first diagnosis in 10-year groups. This analysis is preformed on the Stockholm cohort

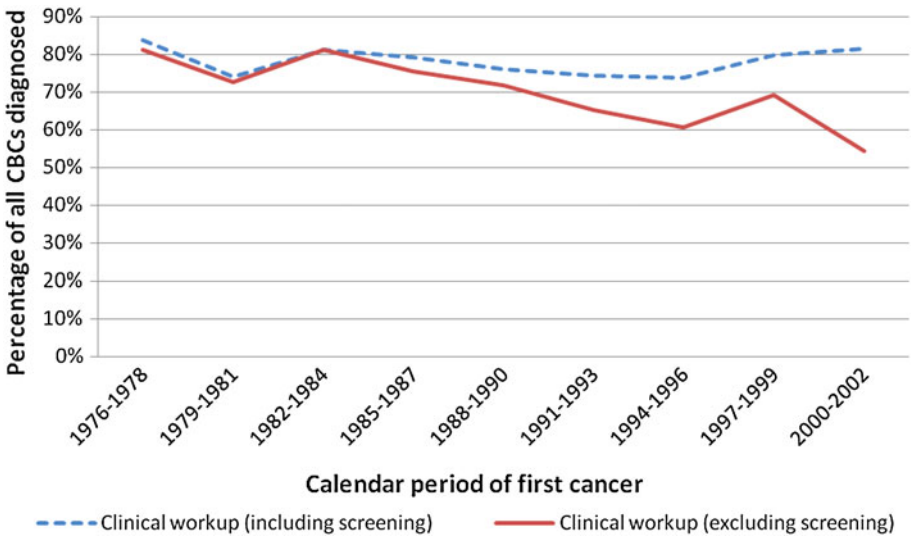

Fig. 2 Proportion of CBCs detected by clinical work-up over calendar period of first diagnosis. Calculations for this graph use the Stockholm cohort

was associated with hormone therapy, but not with chemotherapy. In addition, we found no significant interaction between menopause status and calendar period ($P = 0.23$).

When investigating the proportion of CBCs detected by clinical work-up over calendar period of the first cancer, we could not detect any increasing proportion neither when excluding, nor including, mammographic screening as part of the diagnostic work-up (Fig. 2). Using logistic regression we did not see any trend when including mammographic screening as part of the clinical work-up

Table 3 Mean tumor size (mm) in relation to calendar period of diagnosis

Calendar period of diagnosis	Mean size of first cancer	95% CI	Mean size of second cancer	95% CI
1976–1978	20.8	16.2–25.5		
1979–1981	22.5	19.6–25.3	15.0	11.6–18-3
1982–1984	23.9	18.2–29.7	12.9	10.3–15.6
1985–1987	24.1	18.9–29.3	12.3	9.14–15.5
1988–1990	23.7	17.1–30.3	15.0	11.7–18.4
1991–1993	22.6	15.3–29.9	18.3	12.9–23.7
1994–1996	23.0	19.1–26.9	14.8	12.3–17.3
1997–1999	24.1	19.2–29.0	12.8	10.7–14.9
2000–2002	25.9	17.8–33.9	14.8	11.7–17.8
2003–2005			17.7	10.2–25.1

Mean is calculated for first cancers in the calendar period of first diagnosis and for second cancers in the period of second diagnosis. This analysis is preformed on the Stockholm cohort. *CI* confidence interval

($P = 0.89$), and when not including mammographic screening, we found a significant decreasing trend ($P = 0.0003$).

Finally, as an alternative exploration of whether the sensitivity of the diagnostic work-up has improved, we compared the size of the second tumors across calendar period in the Stockholm cohort. The correlation analysis showed no association ($P = 0.84$) between size of the second tumor and calendar time of the diagnosis of the second cancer. The mean sizes ranged from 15.0 mm (95% CI: 11.6–18.3) in 1979–1981 to 17.7 mm (95% CI: 10.2–25.1) in 2003–2005 (Table 3). The analysis was repeated for synchronous and metachronous cancers separately, in neither of these groups could any decrease in size of the second tumors be shown (P-synchronous = 0.63; P-metachronous = 0.78). Also in the corresponding analysis of first tumor size and calendar time no association was shown.

Interpretations

Our original hypothesis was that the diagnostic work-up of breast cancer patients has improved over the study period, thereby shortening the latency time between the first and second cancer. We found support for this hypothesis in an increased proportion of synchronous cancers and corresponding decreased proportion of metachronous cancers (Fig. 1). Also, logistic regression analysis revealed that odds ratio of being diagnosed with synchronous CBC, compared to metachronous, significantly increased during the study period. However, we found that including clinical work-up in our regression model could not account for the increase in synchronous CBC over time, while including adjuvant therapy, and specifically hormone therapy, could. CBCs were not more likely diagnosed through clinical work-up later in the study period compared to the earlier years and the average tumor size of the second breast cancer has not decreased. Furthermore, we found no correlation between latency time and calendar period of first cancer.

In the Stockholm cohort, the odds of being diagnosed synchronously compared to being diagnosed metachronously has increased by 27% every 5 years (OR = 1.27 95% CI: 1.13–1.42). If this odds ratio was driven by improved clinical work-up, i.e., that the opposite breast is more closely or better examined after a breast cancer diagnosis at present compared to earlier, one would expect it to diminish when controlling for mode of detection, this was not the case in our study (Table 2). Instead, the increasing proportion of synchronous CBC is likely to be explained by adjuvant therapy for the first cancer. We find two possible explanations. Firstly, the use of adjuvant therapy for the first cancer has increased over calendar period [12, 13] and has been shown to decrease the risk of metachronous CBC. In agreement with our findings, some studies have reported that adjuvant hormonal therapy decreases the risk for CBC more than adjuvant chemotherapy [20, 21]. The alternative explanation is that with calendar period, the probability of receiving adjuvant therapy for the first cancer increased to a larger extent for patients with synchronous CBC than for unilateral breast cancer patients (the population at continued risk for metachronous CBC), thus creating an association between being diagnosed synchronously and receiving adjuvant therapy. In our material we see a tendency towards this uneven distribution of adjuvant therapy.

Clinical work-up through mammography might be less efficient for younger women, due to the reduced sensitivity in dense breasts [22, 23], this has been investigated in several studies, with conflicting results [24, 25]. This particular group of young women is also at higher risk of CBC [5]. However, we saw no difference between age groups in our finding of no association of clinical work-up with the increased proportion of synchronous CBCs.

The observed lack of improvement in clinical work-up could possibly be explained by the fact that clinical mammography already early had a high capacity and was frequently used in the breast cancer follow-up. Still, we believe other strategies for follow-up of the opposite breast of breast cancer patients might be considered. MRI and ultrasound examination are currently considered the most promising alternatives [26], with ultrasound having a higher specificity and sensitivity than mammography [27] and MRI is most likely even more efficient, but expensive

[28]. Both MRI and ultrasound have been used in studies of high risk populations (breast cancer patients and close relative of breast cancer patients), showing that they are both efficient in these particular setting [27, 28]. At present, in Sweden, both methods are used only to further investigate breast abnormalities found by mammography or breast palpation.

It has been shown earlier that tumor size is closely associated with mode of detection [29]. In our study the mean tumor size at diagnosis remained constant throughout the study period, supporting the notation that clinical work-up has not improved (Table 3). For comparison, we also show mean size of the first tumor of the CBC patients. It is known from earlier studies that the second cancer tend to be of smaller tumor size than the first cancer, likely due to that they have a different pattern of detection mode [29]. Still, we find the lack of decrease for size of the first tumor somewhat surprising, but possible explanations for this finding lies outside the scope of this paper.

While this investigation was based on the analysis of changing distributions of synchronous and metachronous CBC, it would have been possible to address the question of a changing pattern of CBC over time also by the analysis of incidence patterns. However, such an analysis would be both technically difficult and challenging to interpret because the population at risk is different for synchronous CBC (healthy women) and metachronous CBC (unilateral breast cancer patients). Even with the strategy we choose—an analysis of changing distributions—it would have been possible to express these distributions as a proportion of all breast cancers or as a proportion of all CBCs. Since our primary interest was the CBC-cohort we use the proportion of all CBCs as our main measure. Comfortingly, as the proportion of breast cancer patients that develop CBC within 3 years remained approximately constant over period, these two approaches should not differ. Strengths of our study include the population-based selection of cases, the full coverage of health care registers, which has allowed complete identification and follow-up of CBCs, as well as the almost complete retrieval of medical records (retrieval rate 98%). We also measure effectiveness of diagnostic work-up in two ways; firstly, all CBCs are categorized as either diagnosed by clinical work-up or not, secondly, we assess the time between the first and second cancer and size of the second cancer. These two measures are independent and assess different aspects of the success of the mode of detection; however, it seems pertinent to point out that neither of these measures can reflect the full complexity of diagnosing CBC. While we did adjust for mode of detection in the analysis of the association between synchronous CBC and calendar period, due to the structured guidelines for follow-up of breast cancer patients, there may be a more complicated interplay between timing of the second cancer and the mode of detection. Other limitations of this study are the limited sample size in the Stockholm cohort where we had access to complete information on mode of detection, tumor characteristics and treatment, and also the relatively large proportion of cases with unknown tumor size (14%).

We conclude that the change in proportion of latency groups can seemingly not be explained by earlier detection and a consequential shift from metachronous to synchronous CBCs. A more plausible explanation therefore seems to be a decreasing incidence of metachronous cancer [7] possibly due to adjuvant therapy for the first cancer. The change of latency proportions can be further explained by the increasing incidence of synchronous cancer during the 1970s and 1980s in Sweden [7]. This increase could be in agreement with increasing incidence of unilateral breast cancer. We have shown that the proportion of CBCs detected by clinical work-up is the same now as 25 years ago, and the second breast cancer is neither diagnosed any earlier, nor at any smaller tumor size. This might imply that the diagnostic work-up of CBCs has not improved significantly.

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