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## Review

# Evolving Perspectives in Contralateral Breast Cancer

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**Despite extensive publications reviewing contralateral breast cancer (CBC), the role of screening and preventative measures for contralateral tumours is controversial and optimal clinical management remains undefined. This paper addresses the incidence, the predisposing factors, the prevention and the treatment of bilateral breast cancer based on a review of the literature. Risk factors for CBC include young age at primary breast cancer diagnosis, hereditary breast cancer (due to a germline mutation), familial breast cancer (one or more affected relatives), radiation exposure at a young age, lobular carcinoma *in situ* (LCIS), lobular invasive carcinoma and multicentricity. Retrospective studies suggest that contralateral mammographic surveillance results in the early detection of breast cancer, but no clear survival benefit has been demonstrated. Trials of adjuvant tamoxifen in breast cancer patients have shown a reduction in the incidence of CBC in both pre- and postmenopausal women. In addition, breast cancer patients treated with ovarian ablation and prednisone have significantly reduced CBC versus controls. In patients with primary breast cancer there is no evidence that contralateral breast biopsies or contralateral prophylactic mastectomy reduce mortality. Randomised, prospective trials to determine optimal surveillance, prevention and treatment strategies for the contralateral breast in breast cancer patients have not been conducted. Based on the published literature, contralateral breast surveillance in breast cancer patients reasonably includes breast self-examination, regular physical examinations and annual mammography. In women who have no evidence of distant metastasis at the time of CBC diagnosis, we recommend that the CBC be treated in the same manner as a first breast cancer, taking into account prior local and systemic therapy.** © **1998 Elsevier Science Ltd. All rights reserved.**

**Key words: contralateral breast cancer, hereditary, surveillance, chemoprevention, prophylactic mastectomy**
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## INTRODUCTION

EIGHTEEN THOUSAND women in Canada are diagnosed with breast cancer annually, and approximately one-third die of their disease [1]. Although contralateral breast cancer(CBC) is uncommon compared with the overall incidence of breast cancer, the relative risk of a breast cancer patient developing a contralateral tumour is 1.5–5.5-fold higher than the risk of primary breast cancer in the general population [2–6]. The 20 year cumulative risk of CBC is reported as ranging from 4 to 21% [2–10]. Furthermore, the lifelong probability of CBC is greater in women diagnosed with breast cancer at a young age, mainly due to the longer expected remaining lifetime at risk of developing a CBC (Figure 1).

The majority of CBCs are metachronous (sequential), mammographically detected tumours occurring at a constant rate of approximately 0.5–1%/year throughout a breast cancer patient's life [3, 7, 11, 12]. Although the annual hazard rate of CBC has been estimated to be slightly higher in the first few years following the diagnosis of primary breast cancer [13, 14], it is still less than the annual hazard rate of systemic and local relapse from primary breast cancer, with

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*Table* 1. *Incidence of synchronous contralateral breast cancer (invasive and* in situ*) diagnosed clinically or by mammography within* 6 *months of primary breast cancer diagnosis*

| Author [ref.] | No. of patients | % contralateral cancers |
|---|---|---|
| Israeli [18] | 1337 | FH – 1.0<br>FH + 3.0 |
| Burns [12] | 2231 | 2.1 |
| Prior [19] | 21 967 | 0.4 |
| Hislop [24] | 9000 | 0.7 |
| Fracchia [10] | 4443 | 2.9 |
| McCredie [25] | 3082 | 0.3 |
| Bernstein [20] | 4660 | 1.6 |
| Robinson [22] | 139 932 | 1.8 |
| de la Rochefordiere [23] | 8449 | 1.7 |

FH, family history.

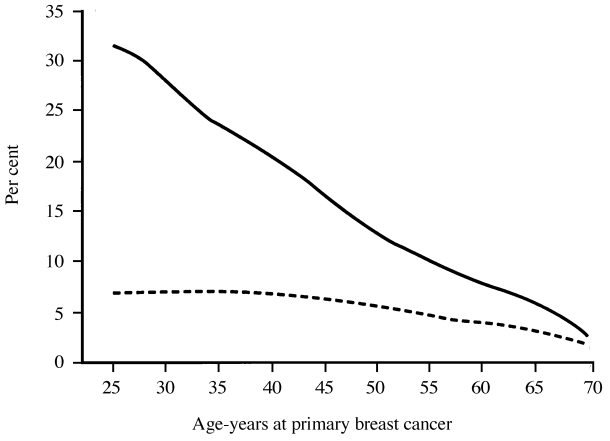


**Figure 1. Cumulative risk of developing a unilateral breast cancer before 75 years of age, based on age (- - - - - -). The lifetime probability of developing a contralateral breast cancer, based on age of diagnosis of primary breast cancer (———). From Storm and Jensen [6] Risk of contralateral breast cancer in Denmark 1943–1980. *Br J Cancer* 1986, 54, 483–492. with permission.**

estimates ranging from 2.5 to 4.3%/year [15]. Nonetheless, CBC is an important issue. With a reduced mortality in breast cancer secondary to primary screening, more patients have a greater life expectancy, resulting in more CBC. Also, given that follow-up investigations in breast cancer patients to detect metastatic disease at a subclinical stage do not improve survival [16, 17], the main emphasis of follow-up should be to detect contralateral cancers that may be cured by early intervention.

Synchronous CBC, detected clinically or by mammography within 6 months of primary breast cancer diagnosis, occurs in very few patients (0.4–3.0; Table 1) [7, 10, 12, 18–24]. In contrast, occult simultaneous cancers, mostly *in situ* lesions, are found in as many as 50% of contralateral mastectomy specimens removed prophylactically from patients with primary breast cancer (Table 2) [25–38]. When lobular carcinoma *in situ* (LCIS) and ductal carcinoma *in situ* (DCIS) lesions are excluded from these series, the incidence of invasive CBC is reduced to 0–5.5%, although Hoffman found an incidence as high as 15% [35]. This rate of CBC is comparable with the 10% incidence of occult primary breast cancers found incidentally in mastectomy specimens removed for benign disease [39, 40]. In addition, autopsy-based reports have found the incidence of asymptomatic CBC, mostly *in situ* tumours, to be 21–68% in patients with a history of breast cancer [41, 42].

The high incidence of contralateral invasive and *in situ* breast cancers detected in some autopsy and prophylactic mastectomy series substantially exceeds the frequency observed in clinical series. This suggests that at least some CBCs either regress or become latent and do not evolve into clinically detectable cancers during a patient's lifetime.

Although one would expect a second metachronous breast cancer to effect prognosis adversely, this has generally not been found to be the case. Recent retrospective and prospective case–control studies have found that overall survival is not compromised by the development of a metachronous breast cancer [6, 7, 12, 43–45]. These studies are variable in the intensity of contralateral breast screening, and some studies include CBC detected by blind biopsies. In addition, many of the studies do not have the power to detect small

*Table* 2. *Incidence of occult synchronous contralateral breast cancer diagnosed from blind contralateral biopsies and prophylactic contralateral mastectomies performed within* 6 *months of primary breast cancer diagnosis*

| Author [ref.] | Sampling procedure | No. of patients | % Contralateral cancers* | % Invasive cancers |
|---|---|---|---|---|
| Smith [26] | Blind biopsy | 95 | na | 2.1 |
| Urban [27] | Blind biopsy | 3012 | 7.6 | 1.7 |
| Wanebo [28] | Blind biopsy | 40 | 11.0 | 2.0 |
| Pressman [29] | Blind biopsy | 247 < 65 years of age | 13.0 | 1.6 |
| Pressman [30] | Blind biopsy | 85 | 12.0 | 0.0 |
| Fenig [33] | Blind biopsy | 314 | 7.3 | 3.5 |
| King [34] | Blind biopsy | 109 | 4.5 | < 1.0 |
| Leis [31] | Blind biopsy | 321 | 7.5 | 3.1 |
| Lee [36] | Blind biopsy<br>Mastectomy | 21 LIC<br>84 LIC | 10.5 | 3.8 |
| Staren [37] | Mastectomy | 29 | 34.4 | 3.4 |
| Leis [32] | Mastectomy | 91 HR | 17.6 | 5.5 |
| Hoffman [35] | Mastectomy | 59 | 37.0 inc CARF | 15.0 |
| Ringberg [38] | Mastectomy | 98 | 50.0 inc LCIS | 5.1 |

*Includes *in situ* lesions. na, not available; LIC, lobular invasive carcinoma; LCIS, lobular carcinoma *in situ*; HR, high risk patients (e.g. family history); CARF, hyperplasia, papilloma, atypical hyperplasia, LCIS and DCIS.

differences in disease-free survival or overall survival. One retrospective study found an increase in the local and distant recurrence rates in patients with CBC compared with unilateral breast cancer (relative risks of 1.7 and 2.2, respectively) [7]. Inherent biases exist in studies of prognosis, since women with metachronous bilateral breast cancer are a select group of patients who have survived long enough to develop a second cancer. Although there is little evidence to suggest a decrease in survival with a diagnosis of metachronous breast cancer, there is also no evidence that failure to identify a CBC prior to its clinical appearance is safe. Thus, there remains controversy regarding the prognosis of patients with a metachronous CBC [46, 47].

Metachronous CBC has generally been found to present at an earlier stage and with a more favourable pathology compared with the primary breast cancer [12], although more advanced stage secondary tumours do occur [48].

In contrast to metachronous breast cancer, synchronous bilateral breast cancer has consistently been associated with a worse overall survival than unilateral breast cancer [20, 48, 49]. The time to the development of a metachronous cancer has also been shown to be a prognostic factor, with cancers developing within the first 3 years increasing systemic recurrence rates and concomitantly decreasing survival [12, 41]. These lesions may represent occult synchronous cancers and/or metastases from the initial primary tumour, which may not always be easily distinguished from a second breast cancer based on clinical and pathological findings.

## RISK FACTORS FOR CBC

Hereditary breast cancer is the most significant factor causing an increased risk of developing bilateral breast cancer [50, 51]. Other factors increasing the risk of CBC include familial breast cancer (as distinct from hereditary breast cancer [52–54], radiation exposure at a young age [55], LCIS [36, 56], lobular invasive carcinoma [36] and multicentric cancer [36, 56]. Young age at primary breast cancer diagnosis is also associated with an increased susceptibility for bilateral breast cancer, mainly due to the increased likelihood of living long enough to develop a metachronous breast cancer [5]. Table 3 lists the relative risks of bilateral breast cancer compared with age-matched control patients with breast

*Table 3. Risk factors for contralateral breast cancer: relative risk of CBC compared with age-matched control patients with breast cancer*

| Factor<br>Variable | Relative risk | 95% Confidence interval | No. of contralateral breast cancers studied | [Ref.] |
|---|---|---|---|---|
| *BRCA1* cumulative absolute risk | | | | |
| by 50 years | 48%* | | 26 | Easton [50] |
| by 60 years | 60%* | (41–73%) | 26 | Easton [50] |
| by 70 years | 64%* | | 26 | Easton [50] |
| Family history | | | | |
| 0 1st or 2nd degree relative | 1.0 | | 212 | Bernstein [52] |
| 1 1st degree relative | 1.9 | (1.2–3.0) | 212 | Bernstein [52] |
| 1 2nd degree relative | 1.3 | (0.8–2.1) | 212 | Bernstein [52] |
| Relative > 45 years of age at diagnosis | 1.5 | (0.8–2.7) | 212 | Bernstein [52] |
| Relative < 46 years of age at diagnosis | 2.7 | (1.5–5.0) | 212 | Bernstein [52] |
| Sister < 46 years of age | 3.4 | (1.6–6.5) | 212 | Bernstein [52] |
| Mother < 46 years of age | 2.4 | (0.1–5.4) | 212 | Bernstein [52] |
| Mother with unilateral cancer | 1.1 | (0.6–2.1) | 212 | Bernstein [52] |
| Mother with bilateral cancer | 2.6 | (1.0–6.3) | 212 | Bernstein [52] |
| Sister < 40 years of age at diagnosis with bilateral breast cancer | 10.5 | (4.0–27.2) | 212 | Bernstein [52] |
| Histopathology of primary cancer | | | | |
| LCIS | 2.6 | (0.8–8.4) | 77 | Healey [7] |
| Lobular (invasive and *in situ*) | 2.0 | (0.8–8.4) | 212 | Bernstein [20] |
| | 1.7 | (1.0–2.1) | 282 | Broet [14] |
| Lobular invasive carcinoma | | 10% @ 10 years | | Lee [36] |
| | 1.6 | (0.7–3.6) | 292 | Horn [57] |
| Tubular invasive carcinoma | na | | 66 | Fisher [43] |
| Multicentricity | na | | 116 | Lesser [56] |
| benign breast biopsy | 1.7 | (1.1–2.5) | 212 | Bernstein [20] |
| | 1.4 | (0.7–2.7) | 292 | Horn [58] |
| Previous radiation | | | | |
| Atomic bomb survivors | na | | 10 | Tokunaga [59] |
| Hodgkin's disease | na | | 7† | Yahalom [60] |
| Adjuvant breast irradiation | | | | |
| all ages | 1.1 | (0.7–1.8) | 292 | Horn [57] |
| | 1.2 | (0.8–1.8) | 655 | Boice [55] |
| age radiation | | | | |
| < 35 years | 2.3 | (0.9–5.7) | 655 | Boice [55] |
| 35–45 years | 1.5 | (0.9–2.3) | 655 | Boice [55] |
| > 45 years | 1.0 | (0.8–1.4) | 655 | Boice [55] |

*Absolute risk. †Excluding 1 LCIS bilateral breast cancer; na, not available; LCIS, lobular carcinoma *in situ*.

cancer. It is important to note that a large relative risk in a young patient may not translate into a large absolute risk, since the baseline risk of bilateral breast cancer in young women is so low.

*Familial and hereditary breast cancer*

Familial breast cancer is defined as breast cancer that develops in a patient with one or more first or second degree relatives with breast cancer, not meeting the criteria for hereditary breast cancer. Familial breast cancer patients have a 2–10-fold higher risk of bilateral breast cancer compared with the general population of breast cancer patients [52–54]. Bernstein and colleagues, in a large age-matched cohort study, demonstrated that the risk of bilateral breast cancer is proportional to the number of primary relatives affected with breast cancer and inversely proportional to their age at presentation [52].

Hereditary breast cancer is breast cancer due to the inheritance of specific germline mutations. Hereditary breast cancer should be suspected in a patient with greater than one relative with breast cancer. It is characterised by: (1) age of onset less than 45 years; (2) bilaterality; (3) an autosomal dominant pattern of inheritance; and (4) a greater frequency of other primary cancers. Between 2 and 5% of all breast cancers are estimated to be hereditary, half of which may be linked to *BRCA1* and *BRCA2* mutations [61]. *BRCA1* mutation carriers have been found to have a lifetime risk of developing primary breast cancer and CBC of 87% and 65%, respectively [50, 51]. One recent study found four to five times more CBC in *BRCA1* mutation carriers as compared with sporadic breast cancer patients [62]. Despite the high frequency of poor pathological features seen in *BRCA1* mutation carriers, survival is similar to sporadic breast cancer patients [62, 63]. Although *BRCA2* is associated with a high lifetime risk of breast cancer (87% by the age of 80 years), there is insufficient documentation of *BRCA2* families to determine the risk of bilateral breast cancer in *BRCA2* mutation carriers.

CBC would be expected to be seen more commonly in other breast cancer susceptibility germline mutations, including *p53* (causing Li Fraumeni syndrome), *ATM* (the ataxia-telangiectasia gene) and *PENT/MMAC1* (responsible for Cowden disease) mutations, as well as other syndromes associated with early onset breast cancer, such as Fanconi's anaemia, Bloom syndrome, and xeroderma pigmentosa. Other than Cowden disease, which has been associated with bilateral breast cancer [64], the risk of bilateral breast cancer with these disorders has not been documented in the literature due to their rarity. Heterozygotes for *AT* have been found to have an increased breast cancer risk [65, 66], and whilst this has been refuted by some authors [67], *AT* heterozygosity may be shown to be associated with an increased risk of bilateral breast cancer in the future. Future knowledge of the genetic basis of breast cancer will likely improve our ability to predict more accurately the risk of bilateral breast cancer development.

*Previous radiation exposure*

A number of studies have demonstrated an increased risk of primary breast cancer in women exposed to ionising radiation, particularly at a young age. Examples include women exposed to atomic bomb explosions [59, 68], repeated chest fluoroscopies [69], multiple diagnostic X-rays for scoliosis [70], treatment for mastitis [71], and radiotherapy for Hodgkin's diseases [72]. Bilateral breast cancer has been reported in women exposed to radiation under 35 years of age, although the magnitude of increased risk has not been clearly documented [59].

Many small case series of bilateral breast cancer following radiotherapy for Hodgkin's disease have been reported [60, 72–77]. The largest review of bilateral breast cancer following Hodgkin's disease radiotherapy is the retrospective review of 37 patients with breast cancer following mantle radiotherapy of Yahalom and colleagues. 7 patients (19%) were found to have contralateral invasive ductal carcinoma, DCIS or colloid carcinoma. Three synchronous and four metachronous tumours were observed over a median follow-up of 3 years following primary breast cancer diagnosis. The patients with Hodgkin's disease were younger than comparable breast cancer patients (40% less than 39 years of age at breast cancer diagnosis) [60]. It is possible that the apparent increased rate of bilateral breast cancer after Hodgkin's disease radiotherapy is related, in part, to the increased risk of bilaterality due to the young age of these patients at breast cancer diagnosis.

Many prospective randomised trials [43, 45, 78, 79] and non-randomised studies [5, 46, 80–82] have found no evidence of increased CBC with postoperative adjuvant breast irradiation, but both higher [13, 14] and lower [47, 83] rates of CBC have been reported in irradiated women. A case–control re-analysis of the data of Storm and associates that originally suggested an increased risk of CBC with radiotherapy, concluded that adjuvant radiotherapy is not a risk factor for CBC [6, 84]. Another case–control study of CBC following adjuvant breast radiation found an increased risk among women who were irradiated before the age of 35 years, although 95% confidence intervals (CI) were wide (RR = 2.3; 95% CI = 0.9–5.7). This risk decreased with irradiation between the ages of 35 and 44 years (RR = 1.5; 95% CI = 0.9–2.3) and with irradiation after 45 years of age (RR = 1.0; 95% CI = 0.8–1.4) [55], but confidence limits overlap. The lack of unanimity regarding CBC and adjuvant breast radiotherapy suggests that the overall contribution of adjuvant radiotherapy to the development of CBC is small, but may be more important in women irradiated at a young age.

*Histopathology of primary breast cancer*

Although LCIS in a primary breast cancer is the most consistent histopathological risk factor for CBC (up to a 3-fold higher risk), multicentricity, tubular and lobular invasive carcinoma are also associated with bilaterality [7, 20, 36, 56]. A history of breast biopsy for benign disease has also been seen more commonly in bilateral breast cancer patients [20, 43, 58].

Oestrogen receptor (ER) and progesterone receptor (PR) status has not consistently been associated with CBC. Mariani and colleagues recently reviewed the influence of ER and PR status on the development of CBC in 1763 patients with node negative breast cancer [85]. High levels of ER appeared to have a protective effect in women under 45 years of age, whereas the opposite was true for women over 45 years of age. High levels of PR were associated with increased CBC in patients with primary ductal carcinomas, but decreased CBC in patients with lobular carcinomas and other histologies. Concordance of ER status between bilateral tumours has been found in some, but not all, reported series [86, 87].

*Stage of primary breast cancer*

It is of interest whether the risk of CBC is influenced by the stage of the initial primary breast cancer. It is conceivable that women with advanced or node positive primary breast cancer might have increased rates of metastatic contralateral breast lesions, which may mask new CBC. Alternatively, patients with early stage breast tumours have a lower risk of metastasis and a longer life expectancy with an increased cumulative rate of CBC. The relationship of stage of primary breast cancer to the development of a CBC remains unresolved [4, 12, 56].

## PREVENTION OF CBC

General approaches to CBC prevention include dietary modification, chemoprevention, ovarian ablation and prophylactic surgery. A detailed discussion on dietary modification is beyond the scope of this paper and we have focused on chemoprevention ovarian ablation and prophylactic surgery.

*Chemoprevention*

There are chemoprevention trials of tamoxifen ongoing in North America and Europe. The National Surgical Adjuvant Breast Project (NSABP) Breast Cancer Prevention Trial, protocol P1, may help to delineate the role of tamoxifen in the primary prevention of breast cancer. 13 388 premenopausal and postmenopausal women were randomised to tamoxifen or placebo. Inclusion criteria were as follows: $\geq 60$ years of age; $\geq 35$ years of age with LCIS treated by local excision only; and 35–59 years of age with a composite increased risk of breast cancer equal to that of a 60-year-old woman (a 1.7% relative risk of breast cancer over 5 years, based on the Gail model [88]). Early reports from this trial are consistent with a risk reduction of primary breast cancer with tamoxifen. However, these data are unpublished to date. Future analysis and follow-up of this study will hopefully provide data regarding the benefits and risks of tamoxifen as a primary breast cancer preventative agent, as well as data on the impact of tamoxifen in the prevention of a CBC.

Another potential chemopreventive agent for CBC is the synthetic retinoid *N*-(4-hydroxyphenyl) retinamide, which is being used in a National Cancer Institute sponsored clinical trial in Europe [89] for CBC prevention in node negative breast cancer patients. No results have been published to date.

Although adjuvant trials were not designed to evaluate the role of systemic treatment as chemopreventive treatment, in the absence of results from chemoprevention trials, it is worthwhile to comment on the adjuvant studies. Adjuvant tamoxifen in patients with primary breast cancer decreases the rate of CBC in postmenopausal women, although its effect in premenopausal women is not as well established. The Early Breast Cancer Trialist's Collaborative Group (EBCTCG) meta-analysis of randomised trials of adjuvant tamoxifen found a significant decrease in contralateral cancer from 2.0 to 1.3% with tamoxifen (a 39% risk reduction). This benefit remained statistically significant for premenopausal women over 50 years of age, but was not as strong in women under 50 years of age who were often excluded from the studies. There was also a trend for increased risk reduction with increased duration of therapy [90]. Many randomised trials of adjuvant tamoxifen have confirmed a 30–60% reduction in metachronous CBC in postmenopausal women [91–96]. An update of the NSABP B-14 protocol [89] of 2644 breast cancer patients with ER positive tumours, at an average follow-up of 53 months, revealed 28 CBC in women treated with tamoxifen compared with 55 second cancers in placebo treated women [92]. In women under 50 years of age, six contralateral tumours occurred in tamoxifen treated patients in contrast to 23 contralateral tumours in placebo treated patients [93]. The Cancer Research Campaign trial, however, suggested a trend for an increase in CBC in premenopausal women treated with tamoxifen compared with premenopausal control patients (4.5% versus 2.5% at 9 years' follow-up) [96].

The EBCTCG meta-analysis of 31 randomised clinical trials did not find a significant reduction in CBC with adjuvant polychemotherapy, 1.8% in the control patients versus 1.7% in the polychemotherapy patients (a non-significant risk reduction of 18%) [90]. In contrast, large case–control studies and retrospective reviews have shown that adjuvant FAC (5-fluorouracil, doxorubicin, cyclophosphamide) and CMF (cyclophosphamide, methotrexate, 5-fluorouracil) chemotherapy may reduce the incidence of CBC [57, 97, 98] and prolong the median latency period between primary breast cancer diagnosis and the development of CBC [98]. Broet and colleagues, in a review of 4748 women with breast cancer, found a relative risk reduction in CBC of 0.54 with chemotherapy [14].

*Ovarian ablation*

Surgical interventions for the prevention of CBC include bilateral oophorectomy and contralateral prophylactic mastectomy. Older studies have suggested that oophorectomy and ovarian ablation by irradiation reduce rates of primary breast cancer [99, 100]. In a recent randomised trial, 702 breast cancer patients aged 35–76 years treated by mastectomy and postoperative chest wall and regional lymph node irradiation were randomised to one of the following groups: no further therapy; ovarian irradiation; or ovarian irradiation plus prednisone (to reduce adrenal as well as ovarian oestrogen production), if $> 45$ years of age. CBC was significantly reduced in breast cancer patients treated with ovarian ablation and prednisone compared with those receiving no further therapy (2.7% versus 8.1%) [101]. This result remained statistically significant among premenopausal patients (4.1% versus 9.7%), but not in postmenopausal women.

*Bilateral prophylactic mastectomy in women at increased risk for primary and CBC*

Bilateral prophylactic mastectomy is a potential intervention for patients at high risk of developing breast cancer. Subcutaneous mastectomies performed in this context leave breast tissue behind with less optimal cancer prophylaxis compared with total mastectomies. Bilateral total mastectomies do not completely eliminate the potential for metachronous lesions to develop [102]. A recent decision analysis comparing prophylactic mastectomy with no prophylactic surgery in *BRCA1* and *BRCA2* mutation carriers concluded that prophylactic mastectomy in a 30-year-old gene carrier leads to 3–5 years of additional life expectancy [103]. The gains in life expectancy declined with increasing age and were minimal for women greater than 60 years of age. These results were most sensitive to the values used for prophylactic mastectomy efficacy (85% risk reduction) and to the rates of breast cancer recurrence (20% recurrence over 10 years). With higher rates of breast cancer recurrence, the gains in life

expectancy for prophylactic mastectomy declined. The relative impact of prophylactic mastectomy versus prophylactic oophorectomy remains to be determined in *BRCA1* mutation carriers.

*Contralateral prophylactic mastectomy*

There are no data evaluating the efficacy of contralateral prophylactic mastectomy in primary breast cancer patients. Breast cancer patients have a decreased life expectancy and, thus, the results of the decision analysis of primary preventative mastectomy in *BRCA1* mutation carriers is not applicable to contralateral preventative mastectomy. There is no current evidence to support routine contralateral prophylactic mastectomy in women with primary breast cancer.

Selected patients with a risk of developing CBC greater than the risk of developing metastatic recurrence potentially would benefit from contralateral prophylactic mastectomy. This group consists mainly of women with hereditary breast cancer diagnosed with good prognosis breast cancer at a young age, with a long life expectancy. In contrast, patients with advanced primary breast cancer and substantial risk of distant disease relapse will less likely benefit from preventative mastectomy. Unlike the annual hazard rate of metastasis, which decreases after several disease free years [15], a constant annual hazard rate results in a large cumulative risk of CBC [14]. The changing ratio of hazard rates with time suggests a larger potential benefit of prophylactic contralateral mastectomy after several recurrence free years from the primary breast cancer diagnosis, when the risk of metastasis from the primary tumour is less. Against this, however, are the data suggesting that CBC might only impact survival if it occurs within 3 years of the initial primary. This supports the concept of an early contralateral prophylactic mastectomy in a patient with a good prognosis primary tumour and a high risk of CBC.

## SURVEILLANCE FOR CBC

Randomised, prospective studies have been conducted to determine the impact of intensive surveillance (physical examination, mammography, blood parameters and roentgenography) versus routine screening (physical examination and mammography) on overall survival and quality of life in primary breast cancer patients [16, 17]. Del Turco and colleagues allocated patients to either routine follow-up (physical examination plus mammography) or intensive surveillance (additional chest roentgenography and bone scan every 6 months) and found no difference in the 5 year overall mortality [16]. The GIVIO randomised trial also compared intensive surveillance with annual mammography and physical examination. At a median follow-up of 71 months, no significant differences were noted in the time to recurrence and overall survival [deaths 20% (intensive) versus 18% (clinical)] [17]. No advantage to intensive surveillance has been shown, and the use of surveillance investigations other than mammography has been discouraged. The American Society of Clinical Oncology recommendations for breast cancer follow-up consist of monthly breast self-examination annual mammography and a history and physical examination every 3–6 months for 3 years, then every 6–12 months for 2 years, then annually [104]. It remains to be evaluated whether breast self-examination, physical examination and bilateral mammography after initial treatment affect the detection of CBC or the survival of breast cancer patients. Randomised controlled trials should be performed to explore definitively the role of contralateral breast surveillance.

*Breast examination*

Breast self-examination is a non-invasive screening intervention which has been shown to result in early diagnosis in some studies [105, 106]. There is, however, mixed literature regarding the value of breast self-examination since some trials have not demonstrated an improvement in clinical staging or reduction in mortality [107, 108]. Whilst its utility in decreasing mortality or morbidity has not been demonstrated for contralateral tumours, it is a non-invasive procedure which should be encouraged.

*Contralateral mammography*

A retrospective comparative study of breast cancer patients treated between 1969 and 1975 (before mammography) and between 1977 and 1984 (after mammography) concluded that mammographic surveillance increased the proportion of *in situ* and stage 1 contralateral tumours diagnosed from 58 to 74% [109]. Flaws with this study include that the regularity and the quality of mammography were not clearly defined and that the cohorts were from different time periods. More recent, larger retrospective studies have found that, although contralateral mammography achieves early cancer detection, survival is not improved [110, 111]. Ciatto and associates reported a series of 175 contralateral metachronous breast cancers. 86 cases were self-referred by women for cancer-related symptoms and 89 were detected by mammography and not clinically apparent. Although detection in the asymptomatic group was associated with better staging, no differences between survival rates were observed between these two groups [110]. Mellink and colleagues studied the breast cancer population in two cities; in one city, surveillance consisted of physical examination and annual mammography ($n = 880$; years 1975–1987) and in the other, surveillance consisted of physical examination only ($n = 411$; years 1971-1984). Although both groups had an incidence of CBC of 3%, patients in the city in which annual mammography was performed, had more contralateral tumours of smaller size and *in situ* carcinoma. The authors noted that no meaningful survival comparisons could be made with their data based on the short duration of follow-up and the limited number of patients [111]. In young women (< 40 years of age) for whom the role of screening mammography is controversial because of the rarity of the disease, the utility for CBC surveillance may be greater. Certainly modern mammographic surveillance has the capability of earlier detection of CBC, but its impact on survival remains to be determined.

There is good evidence that mammographic screening in healthy women over 50 years of age decreases breast cancer death rates and improves survival [112–114]. It is, therefore, tempting to conclude that contralateral breast screening would also lead to a decrease in breast cancer deaths in this population. The benefits of mammographic surveillance in healthy women under 50 years of age remains controversial, due to the decreased sensitivity and specificity of mammography in young women, the potential risk of mammography to the young breast, the decreased incidence and mortality of breast cancer in young women, and the short follow-up of most surveillance studies in premenopausal women. Data on women less than 50 years of age from the Breast Cancer Detection Demonstration Projects (BCDDP) case–control

studies and some randomised studies, suggest that screening mammography results in reduction in death of 20%, although this benefit is not consistently statistically significant [115, 116]. Primary breast cancer in women < 40 years of age is relatively uncommon, whereas CBC is relatively common, so whilst primary screening mammography may not be effective in young women, contralateral follow-up screening mammography in young women with primary breast cancer may be relatively more effective in detecting CBC.

Breast magnetic resonance imaging (MRI) may prove to be valuable in improving the detection of occult CBC in women of all ages in the future, but there is no evidence to support its routine use today.

*Serum markers*

Several serum markers for breast cancer have been studied in regards to breast cancer screening and follow-up. Eskelinen and associates prospectively assessed serum tumour markers in breast cancer patients ($n = 233$), patients with benign disease ($n = 176$) and in healthy control subjects ($n = 215$). The markers examined, including carcinoembryonic antigen (CEA), alfa-fetoprotein (AFP), tissue polypeptide specific antigen (TPS), CA15-3 and neu, were not found to be sensitive or specific enough to be used routinely [117]. The usefulness indices (which takes into account sensitivity and specificity) of these serum tumour markers ranged from 0.004 to 0.04, with only values > 0.35 regarded as useful [118]. Although CA15-3 and CA27.29 have been shown to precede the clinical detection of metastasis in some patients [119, 120], they have not been found to be useful in the detection of low bulk disease (e.g. subclinical local recurrence) [121]. In addition, CA15-3 and CEA were not found to be useful detection tools for diagnosing CBC [122, 123]. Thus, these tumour markers have limited value in breast cancer follow-up and CBC detection at the present time.

*Contralateral breast biopsies*

At the time of primary breast cancer diagnosis, contralateral blind breast biopsies, subareolar biopsies, upper outer quadrant biopsies, and biopsies mirroring the location of the primary cancer have been described [26–34]. Contralateral breast biopsies have been associated with an increase in the detection of occult simultaneous breast cancers, but have not been shown to impact on overall survival [22]. Contralateral biopsies also lead to scaring which may make the clinical and mammographic detection of future breast cancers more difficult. In addition, a negative biopsy report is meaningless, since most of the breast tissue is left *in situ*, and a biopsy positive for LCIS causes concern to the patient and physician with no therapeutic benefit. Thus, there are no data to support the use of screening contralateral breast biopsies in the absence of clinical or mammographic indications for biopsy. With increasing knowledge of the molecular pathogenesis of breast cancer, sequential breast biopsies testing for premalignant molecular markers may have a role in the future for guiding early intervention in women at high risk for contralateral tumours. Selection of particularly high risk individuals for assessment, e.g. prior radiation exposure or *BRCA1* mutation carriers, may be appropriate in this regard.

## TREATMENT OF CBC

Decisions regarding the optimal management of CBC are confounded by the data which show that a metachronous CBC within 3 years of the first primary is likely to affect survival adversely; whereas a CBC detected more than 3 years from diagnosis is not. The impact on survival may be determined by whether the second cancer carries a worse annual hazard of recurrence than the residual risk from the first cancer and whether the risks are additive. There are no prospective data regarding the management of CBC. In our experience, the criteria used to make CBC management decisions have been extrapolated from the criteria used for primary breast cancer patients.

In terms of CBC local management in a patient with no metastatic disease, primary principals guiding optimal surgical and radiation treatment should probably be followed. One practical consideration with adjuvant radiotherapy of the contralateral breast is the possibility of overdosing midline normal tissues, due to the proximity of bilateral breast tangential fields. This potential for overdose can be avoided by careful placement of the contralateral medial field edge [7].

In terms of systemic adjuvant therapy for CBC, decisions will be influenced by a number of factors. Drug resistance induced by prior therapy may influence outcome to therapy for a second breast tumour. Cumulative toxicity, such as cardiac damage or leukaemogenicity from chemotherapy, may also influence the overall value of subsequent treatment. Depending on the interval between the two cancers, treatment with the same chemotherapy or hormone therapy may be considered, although experience from studies of metastatic disease would suggest that appropriate second line chemotherapy or hormone therapy would be more effective [124–127].

## CONCLUSION

In terms of prevention, adjuvant tamoxifen given for primary breast cancer is associated with a decreased risk of CBC. The benefits of adjuvant tamoxifen in premenopausal women and after chemotherapy will become more clear when data from ongoing chemoprevention studies are available. Breast cancer patients with a high risk of CBC, e.g. *BRCA1* mutation carriers, are ideal candidates for chemoprevention studies. Retinoids are also of interest with respect to primary breast cancer and CBC prevention, and should be explored further.

Patients with hereditary breast cancer diagnosed with an early stage breast cancer have an increased risk of developing a CBC and of developing ovarian cancer. This group of patients may be the most appropriate population in which to consider prophylactic contralateral mastectomy and/or prophylactic oophorectomy since an impact on survival may best be documented in such a high risk population. Although a prospective multi-centre randomised study is ideal to study the value of these surgical interventions in young women with hereditary breast cancer, cohort studies may be more feasible. While contralateral prophylactic mastectomy may be considered in high risk patients, the optimal timing of this procedure needs to be addressed. It is not clear if surgery is best performed initially when the overall prognosis is worse or later when survival is more likely. Ovarian ablation (chemotherapy, radiation or surgery induced) as a preventative approach in high risk patients may also have a chance of improving survival.

In terms of surveillance, there are no prospective data to support that contralateral breast screening results in a

decrease in mortality. Thus prospective, randomised trials to address this issue are justified. Until such data become available, contralateral breast surveillance can reasonably include breast self-examination, regular physical examinations and annual mammography for most patients diagnosed with primary breast cancer.

Finally, the efficacy of contralateral breast treatment has not been established. The best method of determining the ideal local and systemic treatments for CBC patients is to undertake randomised trials similar to those performed to determine primary breast cancer treatment. In women who have no evidence of distant metastasis at the time of CBC diagnosis, we recommend that the CBC be treated in the same manner as a first breast cancer. Where adjuvant chemotherapy was given for the first primary breast cancer, the possible reversal of chemotherapy resistance over time should be taken into consideration when choosing whether to use the same adjuvant chemotherapy or another for CBC [126–128]. If CBC occurs while the patient is on adjuvant tamoxifen, an alternative second line hormonal agent may be appropriate.


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