

Review

Epidemiology of Contralateral Breast Cancer¹

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Abstract

Two to 11% of women diagnosed with breast cancer will develop contralateral breast cancer in their lifetime. Women with a first primary are at a 2–6-fold increased risk of developing contralateral breast cancer compared with the risk in the general population of women developing a first primary cancer. The incidence rate of contralateral breast cancer varies from four to eight per 1000 person-years. To assess the risk factors associated with the development of contralateral breast cancer among women with a first primary breast cancer, the epidemiological literature concerning these factors was reviewed and summarized. Studies have shown that a family history of breast cancer, an early age at initial diagnosis, and a lobular histology of the first primary breast cancer increase the risk of developing contralateral breast cancer. Although chemotherapy and tamoxifen therapy may reduce this risk, there are inconsistent results regarding the effects of radiotherapy and the effects of reproductive, environmental and other factors. Additional analytical studies addressing all potential risk factors associated with the development of contralateral breast cancer are necessary in view of the increasing incidence and survival of women with a first primary.

Introduction

The study of contralateral breast cancer is becoming an important public health issue because of the increased incidence of first primary breast cancer and improved survival (1). The first description of contralateral breast cancer was published in 1921 (2). Contralateral breast cancer is of etiological interest because there may be shared risk factors between the first and second primaries (*e.g.*, a family history of breast cancer), whereas other risk factors can be unique to the second primary (*e.g.*, radiotherapy). Understanding the etiology of contralateral breast

cancer should help identify patients who are at an increased risk and alleviate some of the ambiguity surrounding the involvement of environmental, genetic, and hormonal factors influencing the development of breast cancer (3, 4). It should also help monitor the effects of treatment of the first primary breast cancer, especially radiotherapy and chemotherapy.

The objective of this report is to provide an overview of the frequency of contralateral breast cancer and summarize the potential risk factors associated with the development of a second primary breast cancer. The ability to identify which patients are at an increased risk of developing contralateral breast cancer will help both patients and physicians in determining appropriate preventive and protective methods.

Materials and Methods

We undertook a MEDLINE search to find epidemiological studies, including clinical trials, which examined the frequency of a second primary breast cancer and risk factors related to the development of the disease. The reference lists from retrieved studies were manually searched to find additional studies. We also reviewed the recent issues of the major medical journals to find the most recent publications. The articles reviewed and summarized in this report were chosen based on their design, evidence of shared risk factors and treatment effects, and relevance and significance to the etiological understanding of contralateral breast cancer.

Diagnostic criteria for contralateral breast cancer have been characterized (5–7). These criteria offer guidelines to differentiate the diagnosis of a second primary from a metastatic spread of the first primary. Epidemiological studies of contralateral breast cancer differ in the extent to which these criteria are followed. Some studies have included all women with contralateral lesions, whereas others have excluded women with contralateral lesions diagnosed within certain time intervals, *e.g.*, 6 months, 1 year, or even longer. Women with first primary *in situ* lesions may have been either included or excluded. The definition and inclusion of synchronous cancers also vary widely among studies. Lack of universal criteria for a contralateral breast cancer limits the estimation of its frequency and comparison of the available studies.

Available research on contralateral breast cancer is limited by methodological design that complicates the interpretation of results from individual studies and comparisons between studies. Some epidemiological studies report findings qualitatively rather than quantitatively. There is often no comparison performed between a reference group, women with unilateral breast cancer, and the case group, women with contralateral breast cancer. This creates difficulty in determining case status and survival and ultimately the percentage of women at risk (2). We do not use quantitative approaches, *e.g.*, meta-analysis, to combine the results of the studies. Biases can be easily introduced in meta-analysis in such cases because of those study limitations indicated above.

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Table 1 Incidence rate (IR) and SIR of contralateral breast cancer among women with a first primary breast cancer based on cohort data

Author(s) (Ref.)	Location and year ^a	Study subjects	IR (per 1000)	SIR	95% CI (SIR)
Robbins and Berg (5)	United States, 1964	1,458	7.1	5.0	
Haagensen (8)	United States, 1971	626	5.8		
Schottenfeld and Berg (9)	United States, 1971	9,792	6.1	4.5	
Prior and Waterhouse (10)	England, 1978	21,967	4.4	3.0	(<i>P</i> < 0.001)
Mueller and Ames (11)	United States, 1978	3,558	9.3		
Hankey <i>et al.</i> (12)	United States, 1983	27,175	7.1	3.2	
Burns <i>et al.</i> (13)	Canada, 1984	2,231	6.4		
Chaudary <i>et al.</i> (14)	England, 1984	4,656	7.6		
Hislop <i>et al.</i> (15)	United States, 1984	>9,000	3.8		
Harvey and Brinton (16)	United States, 1985	41,109		3.0	(<i>P</i> < 0.05)
Storm <i>et al.</i> (17)	Denmark, 1986	56,237		2.8	2.7–3.0
Murakami <i>et al.</i> (18)	Japan, 1987	9,503		4.2	3.4–5.2
Rosen <i>et al.</i> (19)	United States, 1989	644	8.0		
Brenner <i>et al.</i> (20)	Germany, 1993	9,678		2.48	2.15–2.85
Healey <i>et al.</i> (21)	United States, 1993	1,624	6.8		
Volk and Pompe-Kirn (22)	Slovenia, 1997	8,917		1.4	1.1–1.7

^a Year of publication.

Occurrence

Most investigations of the frequency of contralateral breast cancer frequency have been based upon population-based cancer registries, and others, by selected study groups. The degree of completeness of registration is an important factor affecting the accuracy of the frequency estimation, whereas selection bias may limit the interpretation of the non-population-based data. Definitive diagnosis of contralateral breast cancer is also an area of uncertainty, as indicated above. These difficulties may result in biases in the frequency estimation, which are difficult to assess.

Sixteen cohort studies were identified (Table 1). The incidence rate ranged from 3.8 to 8.0 per 1000 person-years in patients with a first primary breast cancer. The standardized incidence ratios calculated for nine of these studies ranged from 1.4 to 5.0. The cumulative incidence is affected by the length of follow-up period, ranging from 2 to 11% (5, 10, 23–26). Attempts to make a comparison of the incidence rates between studies may not be realistic because of previously mentioned methodological difficulties and lack of consistency.

The risk for women with unilateral breast cancer of developing a second primary is 2–6 times the risk in the general population of developing an initial breast cancer (12). Most studies have shown a SIR³ of three to four (Table 1). Volk and Pompe-Kirn (22) presented a much lower SIR (1.4) compared with other studies, possibly because of misclassification of the disease. Schottenfeld (7) cautioned that the diagnosis of a second primary cancer may be subject to lead-time bias because cancer patients are under closer medical surveillance than the general population, which may result in an inflated SIR.

Risk Factors

Family History

Some studies have demonstrated that a family history of breast cancer is associated with increased risk of contralateral breast cancer (Table 2). The effect of a family history was particularly noted among women with an affected first-degree relative. Studies found that having a sister with breast cancer incurred a greater risk of contralateral breast cancer than having a mother

with breast cancer (3, 26, 28, 31). However, this could be reversed among older women (31). Cook *et al.* (26) showed an odds ratio of 5.27 when both mother and sister were affected; however, the 95% CI was wide (0.97–28.8) because of the small number of subjects. Women with a mother who had bilateral breast cancer and with a sister or mother with younger age at onset were at a particularly elevated risk of contralateral breast cancer (28).

There is some evidence of a relationship between the risk of contralateral breast cancer and time since initial cancer diagnosis. The increased risk of contralateral breast cancer associated with a family history of breast cancer was greater for those with a time interval between the first and second primaries, which exceeded 1 year compared with a time interval of <1 year (15). The risk of second primary breast cancer increased with increasing time since initial cancer diagnosis (3). Other studies, however, found an elevated risk in the first year after initial diagnosis (10, 12, 32).

A family history of other types of cancer, *e.g.*, endometrial cancer and ovarian cancer, may also increase the risk of developing a second primary breast cancer (3, 28). Bernstein *et al.* (28) reported a relative risk of 2.13 (95% CI, 1.04–4.35) for women with a first-degree relative with endometrial cancer and a relative risk of 1.69 (95% CI, 0.42–6.83) for women with a family history of ovarian cancer.

Age at Diagnosis of the First Primary Breast Cancer

A number of studies have found that age at time of first diagnosis is the most important predictor for contralateral breast cancer. The earlier a woman develops an initial breast cancer in her lifetime, the greater the risk of developing a second primary (Table 3). The risk of a contralateral breast cancer showed an exponential decrease with increasing age at diagnosis of first primary, which might due to rapid exhaustion of a susceptible subpopulation (10). Hankey *et al.* (12) found that the incidence density of bilateral breast cancer was 1,005 per 100,000 person-years in the <45 age group, 811 in the 45–54 age group, and 758 in the ≥55 age group during the study period from 1960 through 1975. When age was analyzed by decade, the relative risk for older patients compared with younger patients was 0.79 (95% CI, 0.62–1.10; Ref. 21). A decreased risk with increasing age might be due to a longer life expectancy in younger women (34) and/or be explained by the fact that patients having a

³ The abbreviations used are: SIR, standardized incidence ratio; CI, confidence interval.

Table 2 Family history of breast cancer and contralateral breast cancer (CBC) after a first primary breast cancer in women

Author(s) (Ref.)	Location and year ^a	Study design	Study subjects	Relative risk or odds ratio	95% CI (P)	Comments
Hislop <i>et al.</i> (15)	Canada, 1984	Case-control	275 cases 275 controls	1.6 (<1 yr) 3.1 (>1 yr)	0.6–4.1 1.5–7.1	Marked effect on CBC after 1 year of the first primary
Fisher <i>et al.</i> (24)	United States, 1984	Cohort	1578 women			No significant relationship
Kato <i>et al.</i> (27)	Japan, 1986	Case-control	115 cases 230 controls			No significant relationship
Horn and Thompson (3)	United States, 1988	Case-control	292 cases 264 controls	2.8	1.6–4.9	Increasing family history effect for increasing time since initial diagnosis
Kurtz <i>et al.</i> (25)	France, 1988	Cohort	2850 women (1022 missing)	1.28	(P > 0.10)	Unadjusted
Bernstein <i>et al.</i> (28)	United States, 1992	Cohort	4660 women	1.91	1.22–2.99	Early age at onset in the relative increased the risk
Boice <i>et al.</i> (29)	United States, 1992	Case-control	655 cases 1189 controls	1.8		Statistically significant
Storm <i>et al.</i> (30)	Denmark, 1992	Case-control	529 cases 529 controls	1.44	0.89–2.34	Unadjusted
Cook <i>et al.</i> (26)	United States, 1996	Case-control	234 cases 450 controls	1.96	1.22–5.15	Women with affected sister(s) may have greater risk than those with an affected mother

^a Year of publication.

Table 3 Age at diagnosis of first primary breast cancer and contralateral breast cancer (CBC) in women

Author(s) (Ref.)	Location and year ^a	Study design	Study subjects	Age (yr)	Observed/Expected	95% CI (P)	Comments
Robbins and Berg (5)	United States, 1964	Cohort	1,458 women	<53 53+	8.33 4.94		The split was considered to be close to pre- and post-menopausal
Prior and Waterhouse (10)	England, 1978	Cohort	21,967 women	15–44 45–59 60+	5.6 3.7 1.8	(P < 0.001) (P < 0.001) (P < 0.001)	The risk was extremely high among those of ages 20 to 29 years
Adami <i>et al.</i> (54)	Sweden, 1985	Case-control	1,351 cases 1,351 controls	<50 50+	9.9 1.9	3.8–25.8 1.1–3.2	All incident cases in a defined area were included
Harvey and Brinton (16)	United States, 1985	Cohort	41,109 women	<45 45–54 55+	5.4 3.4 1.3		The trend was less marked for other tumors
Murakami <i>et al.</i> (18)	Japan, 1987	Cohort	9,503 women	<45 45–54 55+	5.9 3.4 3.6	(P < 0.01) (P < 0.01) (P < 0.01)	A similar trend was found for stomach cancer
Brenner <i>et al.</i> (20)	Germany, 1993	Cohort	9,678 women	<50 50+	4.20 2.05	3.27–5.32 1.72–2.43	The incidence of most other cancers was lower than in the general population
Broët <i>et al.</i> (33)	France, 1995	Cohort	4,748 women	<55 55+	RR = 1.40 RR = 1.00	1.10–1.78 (Reference)	Competing risks were considered
Volk and Pompe-Kirn (22)	Slovenia, 1997	Cohort	8,971 women	<50 50+	3.0 1.2	2.1–4.3 0.9–1.4	A similar trend was found for ovarian cancer

^a Year of publication.

family history of breast cancer develop their cancer at an early age (18).

Lobular-type History of the First Primary Breast Cancer

An increased risk of contralateral breast cancer is associated with a first primary breast cancer of lobular histology (Table 4). This may reflect fundamental differences in the biological behavior and/or etiology of tumors having their origin in cells differentiating into lobular rather than ductal cells (32). Dixon *et al.* (38) and Horn and Thompson (36) found that a lobular component of the initial breast cancer, regardless of whether it was invasive or *in situ*, was associated with an almost 2-fold increased risk of developing a contralateral breast cancer, after

adjustment for potential confounders. Fisher *et al.* (24) found that invasive lobular histological type was significantly associated with increased risk of contralateral breast cancer, whereas the number of *in situ* cases was small. Hislop *et al.* (15) found that lobular carcinoma of the first primary was associated with an increased risk of contralateral breast cancer only among the synchronous cases (a time interval between the first and second primaries <1 year) but not among the asynchronous cases. Habel *et al.* (39) studied 2211 women with a primary *in situ* breast cancer and found that the risk was only slightly higher for women with a first primary lobular carcinoma than for women with a first primary ductal carcinoma. There was a markedly elevated risk of contralateral ductal breast cancer,

Table 4 Lobular histology of the first primary breast cancer and contralateral breast cancer among women

Author(s) (Ref.)	Location and year ^a	Study design	Study subjects	Relative risk or odds ratio	95% CI (P)	Comments
Robbins and Berg (5)	United Kingdom, 1964	Cohort	1,458 women	1.42		Relative to overall
Webber <i>et al.</i> (35)	United States, 1981	Cohort	191 women	6.55	(P < 0.01)	<i>In situ</i> breast cancer
Hislop <i>et al.</i> (15)	Canada, 1984	Case-control	275 cases 275 controls	4.3 (<1 yr) 1.0 (>1 yr)	1.2–23.6 0.4–2.5	Lobular histology has no effect for asynchronous cases
Horn <i>et al.</i> (32)	United States, 1987	Case-control	338 cases 336 controls	3.4	1.7–6.9	Adjusted for various factors
Horn and Thompson (36)	United States, 1988	Case-control	292 cases 264 controls	1.8	1.0–3.5	Information available for 251 cases and 243 controls
Bernstein <i>et al.</i> (37)	United States, 1992	Cohort	4,660 women	1.96	1.17–2.74	Adjusted for a number of potential confounders
Broët <i>et al.</i> (33)	France, 1995	Cohort	4,748 women	1.50	1.05–2.18	Association similar in all three models
Cook <i>et al.</i> (26)	United States, 1996	Case-control	234 cases 450 controls	1.47	0.79–2.74	Association stronger among premenopausal women than postmenopausal women

^a Year of publication.

which may result from increased medical surveillance of women diagnosed with breast cancer, especially during the first year after diagnosis (39).

Treatment of the First Primary Breast Cancer

Radiotherapy. Most studies have documented no significant increased risk of contralateral breast cancer after radiation treatment for the initial breast cancer (12, 13, 23, 30, 32, 36, 37, 40–43). Storm *et al.* (30) found no evidence that risk varied with radiation dose, time since exposure, or age at exposure. However, Harvey and Brinton (16) examined the data for 41,109 women diagnosed with breast cancer between 1935 and 1982 and found that women treated with radiation were at a higher risk of developing a second breast cancer than were nonirradiated women (SIR, 3.9 *versus* 2.8). This slight increase was also observed in a case-control study (odds ratio, 1.31; 95% CI, 0.74–1.46; Ref. 26). Murakami *et al.* (18) observed an excess risk of contralateral breast cancer in the radiotherapy group only among those diagnosed at 10 or more years after the first breast cancer diagnosis (SIR, 7.6) compared with the nonradiotherapy group (SIR, 2.9), whereas the overall SIR was 3.8 for the radiotherapy group and 4.8 for the nonradiotherapy group. Boice *et al.* (29) found an increased risk associated with radiotherapy only among women <45 years of age but not among older women. However, Storm and Jensen (17) studied 56,237 women with a first primary breast cancer in Denmark and found that the association between radiation and contralateral breast cancer was obvious for all ages combined but was less obvious among premenopausal (age, <45 years) and perimenopausal (age, 45–54 years) women with primary breast cancer.

Chemotherapy. A number of studies have documented that women who received chemotherapy for the initial breast cancer showed a reduction in risk of developing a contralateral breast cancer (26, 36, 37, 43–46). In a study of 292 cases with an incident contralateral breast cancer and 264 controls who survived unilateral breast cancer, Horn and Thompson (36) estimated an odds ratio of 0.3 (95% CI, 0.1–0.7) for chemotherapy treatment. A cohort study of 4660 women diagnosed with a first

primary breast cancer reported by Bernstein *et al.* (37) showed similar results, that treatment with chemotherapy for the first primary was associated with a lower risk of developing a second breast cancer (relative risk, 0.56; 95% CI, 0.33–0.96). Chemotherapy in early breast cancer may reduce the overall risk of new primary tumors (45, 46). The association with chemotherapy may be modified by body build. Receiving chemotherapy was found to be protective among women of normal or reduced body weight but was associated with an increased risk among overweight women (36, 44).

Tamoxifen. Most clinical trials in the past decade have documented a beneficial effect on the development of secondary breast cancer (Table 5). In a randomized, double-blinded, and placebo-controlled trial of postoperative therapy with tamoxifen in 2644 women with breast cancer, Fisher *et al.* (42) found that the tamoxifen group demonstrated a significant reduction of contralateral breast cancer than the placebo group. On the basis of the data from 75,000 women in 133 randomized trials, a meta-analysis conducted by the Early Breast Cancer Trialists' Collaborative Group (46) showed a reduction of 39% in the risk of development of contralateral breast cancer. Rutqvist *et al.* (47) provided a similar estimation for reduction of contralateral breast cancer with tamoxifen therapy, based on the data from 1846 postmenopausal breast cancer women, and found that the benefit with tamoxifen therapy was greatest during the first 2 years. The studies by the Scottish Cancer Trials Breast Group (48) and the Cancer Research Campaign Breast Cancer Trials Group (49) also found overall beneficial effects of adjuvant tamoxifen on the incidence of contralateral breast cancer. The odds ratio for tamoxifen therapy associated with contralateral breast cancer ranges from 0.5 to 0.6 in both clinical and population studies (50–52). The beneficial effect of tamoxifen therapy may be dependent on menopausal status and disease status. One study performed a subgroup analysis according to menopausal status and found a reduction in the risk of contralateral breast cancer for postmenopausal women and a marginal increase in risk for premenopausal women (49). In a study of 3538 postmenopausal patients who had received surgical treatment for primary breast cancer, Andersson *et al.* (53) found

Table 5 Clinical trials of Tamoxifen therapy treatment and contralateral breast cancer among women

Author(s) (Ref.)	Location and year ^a	Study subjects	% of reduction	Relative risk	Comments
Fisher <i>et al.</i> (42)	United States, 1989	2,644	55 ($P < 0.001$)		Suggests that Tamoxifen may prevent the tumor
Fornander <i>et al.</i> (50)	Sweden, 1989	1,846		0.55 ($P < 0.05$)	Tamoxifen increases endometrial cancer
Rutqvist <i>et al.</i> (47)	Sweden, 1991	1,846	42		Greater benefit during first 2 years
Andersson <i>et al.</i> (53)	Denmark, 1991	3,538	No protective effect		Based on data from high-risk patients
CRC working party (50)	United Kingdom, 1992	1,912		0.49 ($P = 0.08$) 1.41 ($P = 0.44$)	For postmenopausal women For premenopausal women
Oxford Group (46)	United Kingdom, 1992	75,000	39 ($P < 0.001$)		Meta-analysis
Rutqvist <i>et al.</i> (51)	Sweden, 1995	2,729		0.6 ($P < 0.01$)	Tamoxifen increases endometrial and gastrointestinal cancers

^a Year of publication.

a similar incidence rate of contralateral breast cancer in the high-risk tamoxifen-treated group and in the high-risk group not treated with tamoxifen.

Reproductive Factors

Some studies have shown that a later age at the birth of the first child is associated with an increase in risk of contralateral breast cancer (13, 15, 54); however, other studies have suggested that it may protect against development of contralateral breast cancer (3, 27, 55). A longer interval between menarche and the birth of the first child may be a risk factor for the contralateral breast cancer (13). Cook *et al.* (26) found little variation related to menopausal status, except that women who were postmenopausal because of bilateral oophorectomy at initial breast cancer diagnosis had a reduction in the risk of contralateral breast cancer compared with premenopausal women (odds ratio, 0.25; 95% CI, 0.09–0.68). Bernstein *et al.* (37) found a negative association with the number of third trimester pregnancies. Most studies found no relationship between nulliparity and contralateral breast cancer (3, 15, 29, 37, 54), except the one by Sakamoto *et al.* (56). Some studies showed slight protective effects of multiple births on the development of contralateral breast cancer (27, 30, 37, 54), whereas others did not (3, 13, 15).

Body Weight

Kato *et al.* (27) reported a 3-fold increased risk of second primary cancer among women who weighed more than 60 kg compared with those having a body weight of 60 kg or less. Storm *et al.* (30) found that the relative risk was 1.37 (95% CI, 0.94–2.00) for the 25–29 kg/m² group and 1.77 (95% CI, 1.00–3.14) for the 30+ kg/m² group versus the <25 kg/m² group. However, other studies showed no increased risk for contralateral breast cancer in relation to being overweight (3, 15, 37).

Other Factors

An increased risk was observed by Bernstein *et al.* (37) among women who had reported a personal history of benign breast disease before their first primary breast cancer (rate ratio, 1.69; 95% CI, 1.13–2.53) and by Horn and Thompson (Ref. 3; odds ratio, 1.4; 95% CI, 0.7–2.7), whereas two earlier studies showed no clear association between a benign breast disease history and contralateral breast cancer (13, 27).

Having never married was protective in young women, but

the opposite was found among older women (32). A positive progesterone receptor assay and AB blood type were associated with an elevated risk of contralateral breast cancer (3).

Bernstein *et al.* (37) observed no increased risk of contralateral breast cancer in relation to alcohol consumption and cigarette smoking, but Kato *et al.* (27) and Horn and Thompson (3) found somewhat detrimental effects of alcohol and smoking, respectively, on contralateral breast cancer. The use of oral contraceptives was not associated with contralateral breast cancer (3, 13, 15, 37).

Second Malignancies of Other Organs

Women with breast cancer are at an increased risk of developing second primary cancers, not only of the breast but also of other organs. Studies of multiple primary cancers have indicated that for women with breast carcinomas, there is an excess risk for cancers of the colon, ovary, thyroid, and corpus uteri and for malignant melanoma (16, 22, 57). Although these results are not entirely consistent for all studies, the development of a second primary cancer may suggest common risk factors related to the first primary.

Possible factors used to explain the association of multiple primary cancers include genetic influences, endogenous hormones, common environmental exposures, and treatment of the first primary breast cancer. These associations have generally been found to be reciprocal; for example, patients with ovarian cancer as a first primary are at an elevated risk of developing a second primary of the breast (1, 10, 58).

The risks of developing leukemia, cancer of the lung and kidney, and non-Hodgkin's lymphoma after breast cancer is increased and has primarily been attributed to the effects of treatment (1, 16, 58). The importance of shared risk factors and treatment effects associated with multiple primaries has been described (4). Results from studies of multiple primaries may lead to identifying the etiological role of certain risk factors and/or isolating potential risk factors associated with treatment modalities such as radiation and chemotherapy.

Implications for Future Studies

Research on the occurrence of second primary neoplasms can provide useful information regarding shared risk factors for the first and second neoplasms. These studies may also help monitor treatment effects of radiotherapy, chemotherapy, and tamoxifen therapy. There is no clear evidence that any of the following risk factors play a role in the development of con-

tralateral breast cancer: age, race, reproductive variables, alcohol consumption, cigarette smoking, body weight, or use of oral contraceptives.

Treatment effects should continue to be monitored, and future guidelines should be provided for long-term surveillance of surviving cancer patients. Up-to-date and complete cancer registries would facilitate future epidemiological studies.

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