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Second primary cancers of the breast: Incidence and risk factors

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Summary Between 1946 and 1976 over 9,000 women with breast cancer were seen within one year of diagnosis at the A. Maxwell Evans Clinic (AMEC) in Vancouver, British Columbia. By 1978, 275 had a subsequent diagnosis of a second primary in the contralateral breast: 100 were diagnosed within 1 year, and 175 after 1 year of the first primary. Two separate comparison groups of AMEC patients with unilateral breast cancer were selected to identify risk factors for bilateral breast cancer and to determine the incidence. The average annual incidence rates for a second primary in the contralateral breast were 5.0, 4.1 and 3.0 per 1,000 women for women less than 45 years, 45–54 years, and over 55 years of age at diagnosis of first primary breast cancer, respectively. These rates remained stable for at least 15 years after the diagnosis of the first primary. Two risk factors were found for bilateral cancer within 1 year of the first primary, histologic diagnosis of lobular carcinoma and absence of pathologic involvement of axillary nodes; one risk factor was found for bilateral breast cancer after 1 year of the first primary, family history of breast cancer.

With longer survival rates from breast cancer the risk increases that a woman will develop a second breast malignancy. Information is needed about this likelihood and the characteristics of women at high risk, especially when considering such issues as prophylactic contralateral mastectomy. This study was undertaken to determine factors which influence the incidence of second primary tumours of the contralateral breast.

Method

Over 9,000 women had their first histologically confirmed primary breast cancer diagnosed between 1946 and 1976 and were registered for treatment within one year of diagnosis at the A. Maxwell Evans Clinic (AMEC) in Vancouver, British Columbia. Two hundred and seventy-five of these women subsequently had an invasive second primary diagnosed in the contralateral breast prior to November 1978 and they comprised the bilateral cancer group ("cases"). Two comparison groups ("controls") were selected from the remaining women with unilateral breast cancer: one comparison group, the "5% sample", was a randon 5% sample of these women; the second comparison group, the "matched sample", consisted of 275 women individually matched with the cases by age (± 2 years), year of diagnosis of the first primary (± 1 year) and survival (required to be greater than the elapsed time between the diagnosis of the first and second primary breast cancers in the case).

The medical records of the women in the bilateral cancer group and two comparison groups were reviewed in 1978, restricting the observations on risk factors to those available at the time of referral for the first breast primary. None were lost to follow-up. Information was collected on recognised risk factors for both unilateral and bilateral breast cancer and clinical details of the first primary breast cancer. A case-control study design was then used to identify the risk factors associated with bilateral breast cancer. All women with bilateral breast cancer were compared to the matched sample to estimate the relative risk for the various study factors. This was done separately for women with a second primary diagnosed within 1 year ("synchronous cases") and after 1 year ("asynchronous cases") of the diagnosis of the first primary. Analysis was made preserving the matching using classical matched-pair methods (Breslow & Day, 1980).

The incidence of second primary tumours was obtained using a life table method where death or loss to follow up were considered as censored observations (Peto *et al.*, 1977). The study group consisted of the asynchronous cases and the 5% sample. The incidence was calculated separately for women of ages $\leqslant 44$ years, 45–54 years and $\geqslant 55$ years at the time of diagnosis of the first primary in order to see if age at diagnosis affected one's risk

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for a second primary. Age specific incidence rates were also calculated for significant risk factors in asynchronous cases. Differences in incidence were tested for significance using the logrank statistic and its multivariate generalization (Peto *et al.*, 1977).

Results

Of the 275 women with bilateral breast cancer, 100 were synchronous, 60 being diagnosed within one month, and 175 were asynchronous. Differences resulting from matching between the control groups are shown in Table I. Women in the 5% sample tended to be older, with more advanced disease, and diagnosed in more recent years than women in the matched sample.

Risk factors for bilateral breast cancer

The length of the time interval between diagnosing the first and second primaries influenced the type of risk factors for bilateral breast cancer. The risk of diagnosing a second primary within one year of the first primary was significantly elevated for women with a lobular carcinoma and for women with no pathologically determined involvement of axillary nodes. Prior non-contraceptive oestrogen use was of borderline significance (Table II). These three risk factors were independent as the odds ratio for each remained essentially unchanged after controlling for the other two factors.

The risk of diagnosing a second primary after one year of the first primary was significantly elevated for women who reported a history of breast cancer in a first degree relative (Table III). This elevated risk was uniform across different age groups at first diagnosis.

None of the other factors which were examined significantly altered the relative risk of bilateral breast cancer, even after controlling for the significant risk factors. These factors included age at first birth, parity, age at menarche, prior oral contraceptive use, weight, history of other diseases (cancer, benign breast disease, hypertension, thyroid disease), type of early signs or symptoms, multifocal tumours, histologic grade, delay time to diagnosis and to treatment, and location of the tumour.

Incidence of bilateral breast cancer

Figure 1 indicates the observed incidence of a second primary in the contralateral breast for 3 groups, women of ages <45 years, 45–54 years, and $\geqslant 55$ years at the time of diagnosis of the first primary. These rates were restricted to women with at least a one year interval between the diagnosis of the first and second primaries; hence the number of women at risk in the 5% sample was reduced to 376 which gives an estimate of 7,800 for all women at risk in this study population.

There is a non-significant trend of decreasing incidence with increasing age and a clear linear relationship between cumulative incidence and years

Table I Distribution of characteristics related to matching criteria by study group

Characteristic (at diagnosis of the first primary)	*Bilateral breast cancer ("cases")*	*Unilateral breast cancer ("controls")*	
		Matched sample	*5% sample*
Total number	275	275	438
Age (mean years)	53.0	53.0	56.2
Year of diagnosis (%)			
1940s	4	4	3
1950s	24	24	19
1960s	43	43	36
1970s	29	29	42
Clinical stage (%)			
I	61	61	51
II	23	23	22
III	12	9	11
IV	4	7	15
Presence of Invasion (%)			
In situ only	4	3	2
Invasive	96	97	98

Table II Risk factors for synchronous bilateral breast cancer

Factor (refers to first primary)	*Percent with factor*[a] *Cases*	*Matched controls*	*Matched odds ratio*	*95% C.I.*	*P value*
Breast cancer in mother or sister	17%	12%	1.6	0.6– 4.1	0.41
Lobular carcinoma	18%	6%	4.3	1.2–23.6	0.02
Pathologic axillary nodes	34%	48%	0.5	0.3– 1.0	0.05
Prior oestrogen use	20%	10%	2.4	1.0– 6.9	0.06
Late age at first birth[b]	68%	53%	2.7	0.6–15.5	0.23
Prior benign breast disease	12%	10%	1.2	0.5– 3.3	0.82
Multifocal tumours within same breast	7%	2%	3.5	0.7–34.5	0.18

[a]Percent of all cases, and matched controls, with factor; not restricted to discordant pairs.

[b]Late age at first birth dichotomized at <25 years and $\geqslant 25$ years and restricted to women who have given birth.

Table III Risk factors for asynchronous bilateral breast cancer

Factor (refers to first primary)	*Percent with factor*[a] *Cases*	*Matched controls*	*Matched odds ratio*	*95% C.I.*	*P value*
Breast cancer in mother or sister	19%	7%	3.1	1.5– 7.1	0.001
Lobular carcinoma	8%	8%	1.0	0.4– 2.5	1.00
Pathologic axillary nodes	43%	43%	1.0	0.7– 1.5	1.00
Prior oestrogen use	9%	7%	1.3	0.5– 3.1	0.69
Late age at first birth[b]	63%	54%	1.5	0.7– 3.4	0.30
Prior benign breast disease	9%	17%	0.5	0.2– 1.3	0.17
Multifocal tumours within same breast	3%	2%	1.7	0.3–10.6	0.72

[a]Percent of all cases, and matched controls, with factor; not restricted to discordant pairs.

[b]Late age at first birth dichotomized at <25 years and $\geqslant 25$ years and restricted to women who have given birth.

at risk to 15 years. After 15 years, the numbers at risk become too small for reliable estimation. The average annual incidence rates of second primary cancers to the contralateral breast were 5.0, 4.1 and 3.0 cases per 1000 woman-years respectively for women of age <45 years, 45–54 years and $\geqslant 55$ years at the time of diagnosis of the first primary. These differences were not significant. Figure 1 also shows the expected incidence of a second primary based on the 1971 age specific incidence rates of primary breast cancer in women in British Columbia (Cancer Register, 1975) and the age and survival distribution of the 5% sample. As expected, the differences in the expected incidence rates between age groups were large, much larger than the differences in the observed incidence rates.

The age adjusted incidence of asynchronous bilateral cancer was then determined for women with, and without, a history of breast cancer in the mother or sister (Table IV). In general the rates

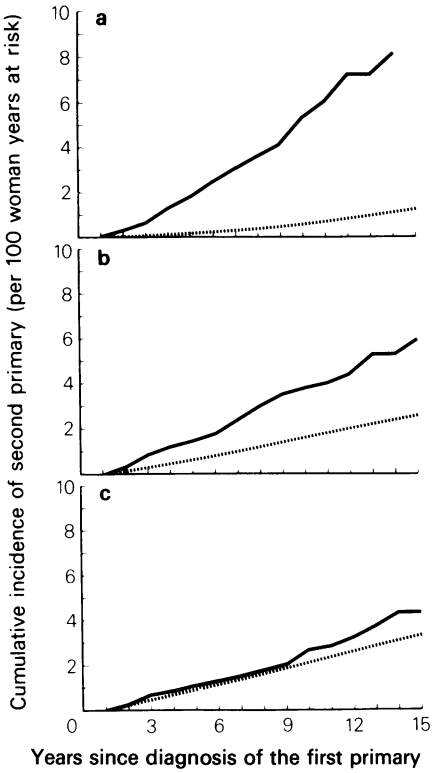

Figure 1 Incidence of a second primary in the contralateral breast in women clinically disease-free one year after the diagnosis of the first primary breast cancer by age at diagnosis of the first primary (<45 years, 45–54 years, ≥55 years). Solid line, observed rate; broken line, expected rate. Estimated number of women at risk at 1, 5, 10 and 15 years, respectively: (a) <45 years of age, 1,374, 796, 435, 244; (b) 45–54 years of age, 2,362, 1,235, 574, 265; (c) ≥55 years of age, 3,959, 1,827, 711, 244.

were reasonably stable over time with approximately a doubling of risk in women with a positive family history of breast cancer.

Discussion

Incidence rates for second breast primaries have been reported to range from 3–10 cases per 1000 woman-years and from 0.3–0.9% of women with breast cancer have a second primary diagnosed within 1–6 months of the first primary (Table V and VI). Random biopsy and autopsy studies have found that the prevalence of microscopic second primary tumours is much higher, ~12% (Urban *et al.*, 1977; Berge & Ostberg, 1974).

Methodological difficulties limit the interpretation of some of these studies. Such difficulties include the use of small selected study groups, differing age distributions among the study groups with non-standardized incidence rates, and varying lengths of time between the diagnosis of the first and second primary tumours. We attempted to overcome some of these methodological problems. Our study was based on a population of over 9,000 women with over 30 years of follow-up which was analysed by a life table method.

Since the study groups are selected from patients who are referred to a tertiary care treatment centre and since the likelihood of referral could be affected by the suspicion of a second primary, the incidence of bilateral breast cancer may be over estimated. This referral bias is indicated by the high frequency of "simultaneous" second primaries (i.e. diagnosed within 1 month of the first primary) that was observed in this study as compared to other studies in the literature. We tried to minimize the

Table IV Age adjusted incidence of bilateral breast cancer by time interval between diagnosis and family history

		Time interval between diagnosis of first and second primaries			
Family history		*1–5 yrs*	*5–10 yrs*	*Over 10 yrs*	*Total over 1 yr*
No breast cancer in mother or sister	Incidence[a]	3.1	4.3	3.7	3.5
	No. at risk[b]	479	244	107	
Breast cancer in mother or sister	Incidence[a]	5.6	4.1	14.0	6.2
	No. at risk[b]	72	37	16	

[a]Age adjusted incidence rate per 1,000 woman years at risk standardized to the years at risk of the total population (i.e. 5% sample).

[b]Number of women at risk at the beginning of the time interval between diagnosis of the first and second primaries.

Table V Incidence of a second primary to the contralateral breast

Reference	*Study population*	*Number at risk (woman years at risk)*	*Incidence (per 1000 woman years)*
Population based studies			
Prior & Waterhouse, 1978	Birmingham, England 1936–1964	21,967 (91,233 WYR)	4.4
Mueller & Ames, 1978	Syracuse, New York 1956–1974	3,558	8–10, to at least 15 years
Hospital based studies			
Haagensen, 1971	Personal series 1935–1957	626 (6,200 WYR)	5.8
Robbins & Berg, 1964	Memorial Hospital (N.Y.) 1940–1943 followed to 1963	1,458 (12,818 WYR)	7.1, to at least 20 years
Fukami *et al.*, 1977	Tokyo 1946–1975	3,365 (26,771 WYR)	3.4, to at least 18 years
Schottenfeld & Berg, 1971	Memorial Sloan-Kettering 1949–1962	9,792 (40,676 WYR)	6.1
McCredie *et al.*, 1975	Ontario Cancer Treatment & Research Foundation 1953–1971	1,489, excluded subsequent metastases or recurrent disease (~50%)	~10, to at least 20 years
Current study	A. Maxwell Evans Clinic 1946–1976	over 7,800 survived at least 1 year without a second breast primary (over 45,000 WYR)	3.8, to at least 15 years

effect of referral biases by restricting our study to women seen at the AMEC within 1 year of diagnosis of the first primary and then by analyzing the data separately for patients with a second primary diagnosed within 1 year (synchronous cases) and after 1 year (asynchronous cases) of diagnosis of the first primary. Hence this bias should be limited to the findings for synchronous cases.

Another potential source of bias relates to the development of metastatic disease. Since the diagnosis of a second primary is clinically of limited importance in a patient with metastatic disease, one could expect a less extensive search for second primary tumours in patients with known metastatic disease. It could be argued that for this reason persons should be censored at the date of diagnosis of metastatic disease. This was not done because this date was not always recorded. We would expect that this bias would result in underestimating the incidence rate of bilateral breast cancer because second primary tumours may be missed.

The following risk factors have generally been associated with an increased risk of bilateral breast cancer: an early age at diagnosis of the first primary (Robbins & Berg, 1964; Leis & Urban, 1978; Prior & Waterhouse, 1981; Adami *et al.*, 1981; Slack *et al.*, 1973; Hubbard, 1953); a family history of breast cancer (Armstrong & Davies, 1978; Fukami *et al.*, 1977; Leis & Urban, 1978; Hubbard, 1953; Harris *et al.*, 1978), especially breast cancer in the mother (Anderson, 1977); lobular carcinoma (Kiang *et al.*, 1980; Lewison & Neto, 1971; Robbins & Berg, 1964; Webber *et al.*, 1981); and multiple tumours within the same breast (Robbins & Berg, 1964; Leis & Urban, 1978). Conflicting results have been found for histologic grade (Robbins & Berg, 1964; Adami *et al.*, 1981), size (Robbins & Berg, 1964, Slack *et al.*, 1973) and stage (Fukami *et al.*, 1977; Robbins & Berg, 1964; Leis & Urban, 1978) of the first primary. Age at

Table VI Frequency of a "simultaneous" primary to the contralateral breast

Reference	*Number at risk*	*Second primary*	*Definition of "simultaneous" second primary*
Prior & Waterhouse, 1978	21,967	0.4%	Diagnosed within 1 month of the first primary
Mueller & Ames, 1978	3,558	0.9%	Diagnosed within 6 months of the first primary
Haagensen, 1971	626	0.6%	Not defined
Robbins & Berg, 1964	1,458	0.3%	Diagnosed before removal of the first primary
Fukami *et al.*, 1977	3,365	0.7%	Not defined
Schottenfeld & Berg, 1971	9,792	0.6%	Diagnosed during treatment of the first primary
McCredie *et al.*, 1975	3,082	0.3%	Diagnosed within 6 months of the first primary
Carroll & Shields, 1955	review of 14 studies	1.4%	No consistent definition
Current study	9,000	0.7%	Diagnosed within 1 month of the first primary
		1.1%	Diagnosed within 1 year of the first primary

first birth, a well established risk factor for breast cancer, has not been associated with an increased risk of bilateral breast cancer (Adami *et al.*, 1981).

We found that a family history of breast cancer was associated with an increased risk of bilateral breast cancer, but only if the time interval between the first and second primaries exceeded one year (asynchronous cases). The reason for the absence of an association for tumours diagnosed less than one year apart (synchronous cases) in unclear. These synchronous second primaries, however, were associated with three independent factors, lobular carcinoma, absence of pathologic involvement of the axillary nodes and prior oestrogen use. The reduced risk in women with pathologic node involvement probably results from underdiagnosis of second primaries in women with metastatic disease.

Factors which influence the length of survival, such as age, stage and histologic grade, could affect the likelihood of developing a second primary and hence could be identified as important risk factors for bilateral breast cancer. We have minimized the effect of these prognostic factors by matching cases and controls on survival, at least to the diagnosis of the second primary. This effect is limited to asynchronous breast cancer for the length of survival should not influence the risk of synchronous bilateral breast cancer.

Although not statistically significant, the annual incidence of a second primary tended to decrease with later ages at diagnosis of the first primary. This has been reported in other studies. Unlike these earlier studies which compared observed numbers of second primaries with expected numbers as determined from age specific incidence rates for breast cancer, this study compared the observed incidence of second primaries at various age categories.

In conclusion, this study has found that the risk of breast cancer in the contralateral breast in women with a personal history of breast cancer is greater than the risk of breast cancer in the general population. This risk is stable over time, at least to

15 years after diagnosis of the first primary. Other risk factors for bilateral breast cancer are dependent on the length of time interval between the diagnosis of the first and second breast primaries.

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