Bilateral breast cancer in northern Alberta: risk factors and survival patterns

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Of 2231 women with stage I, II or III breast cancer who were registered and seen between 1971 and 1979 and followed to the end of 1981, 48 (2.2%) had synchronous and 58 (2.6%) asynchronous bilateral breast cancer. The unadjusted incidence rate for a second breast cancer was 6.4/1000 breast-years at risk, compared with a rate of 0.70 for the risk of a first breast cancer in women. When calculated from the date of diagnosis of the first breast cancer the survival rate was better for the group with asynchronous disease than for the group with synchronous disease or for a group with unilateral disease, but when calculated from the date of diagnosis of the second cancer the rate was the same in all three groups. Comparison of known risk factors showed a significant association between the development of bilateral cancer and a later age at the birth of the first child and a longer interval between menarche and that birth. There was a trend towards greater age and more stage III cancer in the group with synchronous disease. There was no correlation between receiving radiotherapy for the first breast cancer and development of the second cancer. Annual mammography and clinical examination of asymptomatic women at a cancer centre resulted in the detection of a significantly higher proportion of minimal breast cancers in the second breast compared with the first. Such screening practices should be even more valuable in the earlier detection of unilateral breast cancer in asymptomatic women who have not had breast cancer.

Parmi 2231 femmes atteintes de cancer du sein au stade I, II ou III dénombrées et vues entre 1971 et 1979 et suivies jusqu'à la fin de 1981, 48 (2,2%) avaient un cancer du sein bilatéral synchrone et 58 (2,6%) un cancer du sein bilatéral asynchrone. L'incidence non corrigée d'un deuxième cancer du sein a été de 6,4/1000 années-seins, comparativement à un taux de 0,70 pour le risque d'un premier cancer du sein chez la femme. Lorsque calculé à partir de la date de diagnostic du premier cancer du sein le taux de survie a été meilleur pour le groupe à cancer asynchrone par rapport aux groupes à cancer synchrone ou à cancer unilatéral. Toutefois, lorsque le taux de survie a été calculé à partir de la date de diagnostic du second cancer il s'est avéré le même pour les trois groupes. La comparaison des facteurs de risque connus a révélé une association significative entre le développement d'un cancer bilatéral et un âge plus avancé à la naissance du premier enfant ainsi qu'un intervalle plus long entre la première apparition des règles et cette première naissance. Il y avait une tendance à un âge plus avancé ainsi qu'aux cancers au stade III chez le groupe à cancer synchrone. On n'a constaté aucune corrélation entre la radiothérapie d'un premier cancer et le développement du second. Une mammographie et un examen clinique annuels des femmes asymptomatiques dans un centre de dépistage du cancer a permis la découverte d'un pourcentage significativement plus élevé de petits cancers du sein dans le second sein que dans le premier. De telles pratiques de dépistage devraient être encore plus utiles pour déceler précocement les cancers du sein unilatéraux chez les femmes asymptomatiques qui n'ont pas encore eu le cancer du sein.

The objectives of this study were to determine the incidence of bilateral breast cancer in northern Alberta, to compare the survival of women with unilateral and bilateral disease and to assess the relative importance of known risk factors for breast cancer in such women. The relative value of physical examination and mammography in screening the second breast was compared with the value of similar procedures in women presenting with unilateral breast cancer. It was hoped that the knowledge derived from this study would be valuable in planning screening programs for other high-risk groups as well as counselling women about prophylactic removal of the second breast.

Methods

We used definitions of synchronous and asynchronous breast cancer similar to those of Haagensen.[1] These require that synchronous breast cancer occur within 6 months of the first diagnosis and that asynchronous breast cancer occur 6 months or more after the first diagnosis; in both instances there must be no evidence of local recurrence or metastases prior to and up to 6 months after the second diagnosis.

Our data came from the breast cancer registry in Alberta,[2] which includes more than 80% of all patients with breast cancer in northern Alberta, almost all of whom had been interviewed, examined and followed at the Cross Cancer Institute, Edmonton. The second breast was screened by clinical examination and mammography at the time of initial presentation and annually thereafter. Seven percent (156) of the patients had chosen or their doctors had advised them to be followed

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elsewhere at various times after their initial presentation. In order to include all the patients registered with a second breast cancer during the years of this study, six of these patients have been included in the asynchronous bilateral group although they failed to have annual mammography after deciding to be followed elsewhere.

Three groups of patients were defined: those with synchronous bilateral breast cancer, those with asynchronous bilateral breast cancer and a comparison group with stage I, II or III[3] unilateral breast cancer who had survived for 6 months or more disease-free. All the patients had been registered between 1971 and 1979 and followed to the end of 1981 to ensure a minimum follow-up period of 2 years. The 6-month disease-free interval for the comparison group was used to minimize the bias inherent in the definition of bilateral disease.

More than 20 pathologists, who used no standardized system of classification, reported on the biopsy specimens, so a detailed pathological review was not possible. Because of this, only a broad classification of noninvasive or invasive carcinoma was used for this report. Noninvasive was either intraduct carcinoma or lobular carcinoma in situ, and invasive was infiltrating duct or infiltrating lobular or "other". Minimal breast cancer was defined as either a noninvasive carcinoma of any size or an invasive carcinoma less than 1 cm in diameter.

Censored survival curves were used to compare survival and disease-free survival from the date of the first diagnosis of breast cancer.[4] For asynchronous bilateral cancer, survival was also calculated from the date of diagnosis of the second breast cancer.

The risk factors studied were those known to affect breast cancer in northern Alberta.[5,6] The percentage of patients who received radiotherapy as part of their initial treatment was estimated for the comparison group and the asynchronous group, as this therapy might have been a causative or additive factor in the development of a second malignant tumour. Significance was determined with the chi-square test.

Results

Of the 2231 patients with stage I, II or III breast cancer registered between 1971 and 1979, 48 had synchronous bilateral breast cancer; of the remaining 2183, 58 patients with asynchronous bilateral cancer had been registered up to the end of 1981 (Table I). Six of the asynchronous cases had been followed elsewhere, and in the remaining 52 the diagnosis had been made during 6482 annual examinations at the Cross Cancer Institute. Only one patient had been lost to follow-up. The ratio of benign to malignant disease for breast lesions that underwent biopsy was 4.7:1. The interval between the two diagnoses in the asynchronous cases ranged from 7 months to 10 years, these limits being defined by the study protocol. The annual number of asynchronous cases increased from 2 in 1972 to 13 in 1980. Fig. 1 shows the proportion of patients in each group according to the year of diagnosis of the first cancer.

Between 1971 and 1979 there were 6013 breast-years at risk, as calculated from the total number of annual examinations of the second breast, excluding the 13 cases of asynchronous cancer diagnosed in 1980 and 1981 and the 6 diagnosed elsewhere and excluding the breast-years lost to our follow-up by the patients who were followed elsewhere. Thus, there were 39 cancers detected in 6013 breast-years, for an unadjusted rate of 6.4/1000 breast-years at risk. This compares closely to the rate of 7.1 given by Robbins and Berg.[7] In 1978 the rate of new breast cancer in the province was 0.70/1000 breast-years (an approximation based on two breasts per woman being at risk, half the female population being older than 29 years and breast cancer being rare in those less than 30 years old).

Table I—Incidence of bilateral stage I, II or III breast cancer and ages among northern Alberta patients whose first breast cancer was registered between 1971 and 1979 inclusive, who survived more than 6 months and who were followed up for 2 to 10 years

Patient group; no. (and %)	Age (yr)		
	Extremes	Mean	Mode
Unilateral comparison, 2060 (92.3*)	29; 97	57	47
Bilateral synchronous, 48 (2.2*)	40; 85	60	65
Bilateral asynchronous,† 58 (2.6‡)	28; 90	57	46

*Percentage of all 2231 registered breast cancer patients.
†Six patients were followed elsewhere.
‡Percentage of all registered breast cancer patients except the 48 with bilateral synchronous cancer (i.e., 2183). The total group of patients with bilateral cancer (106) represented 4.8% of all 2231 registered patients.

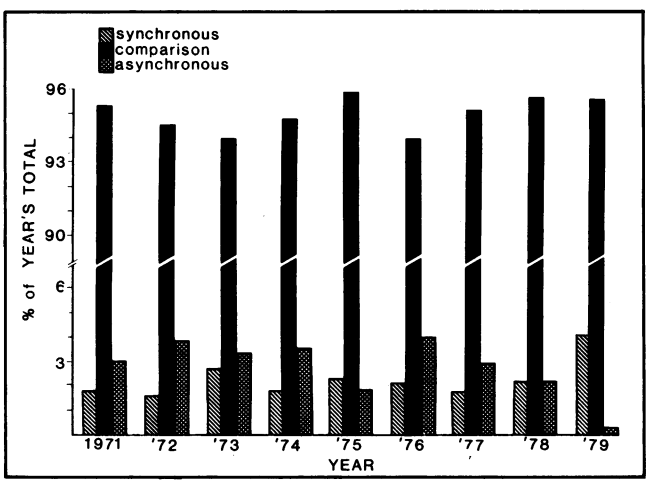

Fig. 1—Proportion of patients with unilateral breast cancer (comparison group) and bilateral breast cancer (synchronous and asynchronous groups) according to year of diagnosis of first cancer.

Table II—Stage of breast cancer* when diagnosed

Stage	Patient group; no. (and %)		
	Comparison	Synchronous	Asynchronous
I	545 (26)	10 (21)	20 (35)
II	845 (41)	24 (50)	31 (53)
III	368 (18)	14 (29)	7 (12)
IV	302 (15)	0	0

*The larger tumour in the synchronous cases.

The patients with asynchronous cancer and the comparison group had lower modal and mean ages at the time of diagnosis than the patients with synchronous cancer (Table I), and a smaller proportion of the stage III tumours occurred in those with asynchronous cancer (Table II).

There was no correlation between the sites of the first and second cancers (Table III). In 64% of the few tumours occurring at the same site, this was the upper outer quadrant.

The histologic type of the tumour was the same for both breasts in 37% of the patients. For the first breast affected in the bilateral cases (or the larger cancer in the synchronous cases) the tumour was either infiltrating duct or scirrhous carcinoma in 48% of the patients and invasive or in-situ lobular carcinoma in 13%. For the second breast affected the corresponding proportions were 54% and 19%. In the comparison group 10% of the patients had lobular carcinoma. Noninvasive tumours accounted for significantly more ($p < 0.001$) of the cancers in the second breasts affected than in either the first breasts affected or the comparison group, the proportions being 30%, 7% and less than 1% respectively. Minimal breast cancer occurred in less than 1% of the comparison group and of the first breasts affected in the patients with bilateral cancer but in 23% and 53% of the second breasts affected in those with synchronous and asynchronous cancer respectively.

The proportion of cancers detected only by mammography (rather than only by physical examination or by both methods) increased from 2% in the comparison group and the first breasts of those with bilateral disease to 35% and 65% in the second breasts of those with synchronous and asynchronous disease respectively. Physical examination alone detected 6% of the cancers in the comparison group and the first breasts of the patients with bilateral disease but 29% and 25% of the cancers in the second breasts of those with synchronous and asynchronous disease respectively. For asynchronous disease these figures refer only to the patients regularly followed at this clinic for whom data were available. Of the six patients not so followed only one had minimal breast cancer (found accidentally during prophylactic mastectomy); the rest presented with lumps of various sizes that the patients had found themselves, and in two of these, lymph nodes were involved.

Of the 52 regularly screened patients only 5 (10%) had axillary node involvement with the second (asynchronous) cancer. The history in each of these patients was very similar: progressive changes detected by clinical examination were attributed to "fibrocystic disease", and one or more mammograms were interpreted as showing "gross dysplasia"; therefore, diagnosis was delayed.

Risk factors compared in the three groups were age at diagnosis, at menarche, at birth of the first child and at menopause, family history, hormone usage, parity, lactation and previous tonsillectomy. Of these, only later age at the birth of the first child and a longer interval between menarche and that birth were more common in the bilateral than in the unilateral cases, but because of the small sizes of the groups with bilateral disease these results were only marginally significant. More patients in the asynchronous than in either of the other two groups had a positive family history, but the difference was not significant. The proportion of premenopausal patients in the asynchronous group (35%) was slightly higher than that in the comparison (30%) and synchronous (23%) groups. Although 37% of the comparison group compared with 45% of the group with asynchronous disease had received radiation therapy for the first breast cancer, this difference was not significant as a risk factor.

Censored survival and censored disease-free survival from the date of the first diagnosis of breast cancer (Figs. 2 and 3) were similar for the comparison and synchronous disease groups, but the rates for the group with asynchronous disease were significantly better ($p < 0.01$). When survival and disease-free survival for the asynchronous cases were calculated from the date of diagnosis of the second cancer there was no significant difference among the three groups.

The nine patients in the group with asynchronous

Table III—Tumour sites in cases of bilateral breast cancer

Breast quadrants	Patient group; no. (and %)	
	Synchronous	Asynchronous
Same	13 (27)	6 (10)
Different	32 (67)	46 (80)
Unknown	3 (6)	6 (10)
Total	48 (100)	58 (100)

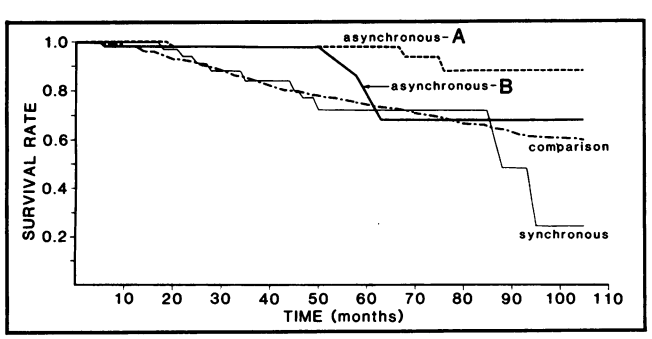

Fig. 2—Censored survival of each study group. Difference between synchronous and asynchronous groups, with survival of latter calculated from anniversary of first diagnosis (A) rather than second (B), significant at $p < 0.01$.

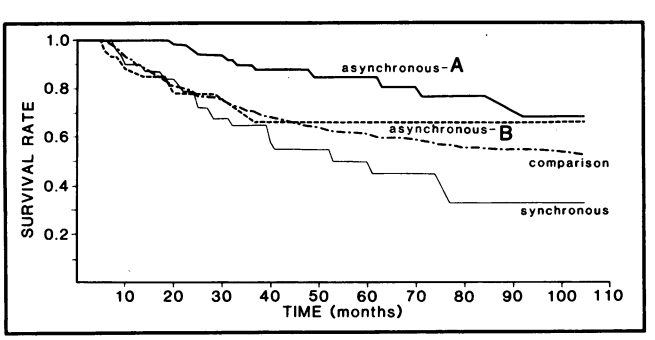

Fig. 3—Censored disease-free survival of each study group. Difference between synchronous and asynchronous groups, with survival of latter calculated from anniversary of first diagnosis, significant at $p < 0.01$.

disease in whom local recurrence or metastases developed and whose poorer survival affected the overall survival for the group were looked at in greater detail. Only one patient in this subgroup had minimal breast cancer in the second breast affected; she died 4 years later from bilateral ovarian cancer. The pathological findings were reviewed, and the consensus was that the ovarian cancer was an entirely new primary tumour. In three of the patients in whom metastases developed the second breast cancer was diagnosed relatively late; that is, there was between 3 and 12 months' delay owing to the mistaken impression that the patient had a cyst or fibrocystic disease. Five other patients with recurrent disease were followed elsewhere and had not had mammography regularly.

Discussion

In 1964 Robbins and Berg[7] published a review of bilateral breast cancer based on their own patients and the literature. They stressed the difficulties of comparing series because of the differences in definition of bilaterality that had been used over the years, variations in length of follow-up and the difficulty of distinguishing metastatic disease from primary tumours. Harrington[8] had stated in 1946 that 50% of second true primary tumours may be concealed in the second breast of a patient with metastatic breast cancer. At the time of Robbins and Berg's report mammography was in its infancy and had obviously not been used to diagnose many, if any, of the cancers in their review, most of which had been relatively advanced at the time of diagnosis.

The incidence of bilateral breast cancer in the northern Alberta population over the study period was approximately the same for synchronous and asynchronous disease (2.2% and 2.7% respectively). The numbers of patients with bilateral breast cancer would have been greater if the follow-up period had been longer than 2 to 10 years and if patients with stage IV cancer (which accounted for 8% of all cases of breast cancer registered) had been included. It is surprising that the number of asynchronous cases has not decreased steadily with later date of diagnosis and the correspondingly shorter period of follow-up. That it has not reflects a greater awareness of possible cancer in the second breast as well as improvement in diagnostic skills, but it should plateau with time as each year's cohort decreases owing to deaths. Other centres have reported similar results if one allows for differences in methods and length of follow-up. The Mayo Clinic reported a 2% incidence of synchronous disease detected by clinical examination, mammography and mirror-image biopsy,[9] whereas a Johns Hopkins Hospital study found a 1.7% incidence of synchronous disease, but the diagnostic methods were not described.[10] The Johns Hopkins study was of a small series with a higher incidence of asynchronous disease (6.9%) than we found; however, the follow-up period was longer than in our series. The M.D. Anderson Hospital and Tumor Institute study of patients with stage I and II breast cancer showed double the proportion of asynchronous cases that we found, but those patients were followed for 20 years.[11]

Urban and collaborators[12] have advocated contralateral breast biopsy for all patients with breast cancer at the time of a first mastectomy, basing this suggestion on their finding of bilateral synchronous cancer (most cases being of minimal and noninvasive cancer) in 12.5% of patients. Their findings are surprising, as this rate for synchronous cancer is higher than the rate for all the second breast cancers (synchronous and asynchronous) that we detected in 10 years and higher than the rate of 1% per year reported by McCredie and coworkers.[13] In view of our finding of no correlation between the sites of the first and second cancers, it is even more surprising that Urban and collaborators detected, presumably with a random mirror-image biopsy, cancer in the opposite breast in 23 (7.6%) of 301 patients with no signs or symptoms in that breast, and Leis,[14] using a similar technique, reported a rate of 8.5% for synchronous cancer. Fratkin[15] observed the same lack of correlation between the sites that we have recorded.

Leis[16] has also reviewed the incidence of synchronous disease reported by several authors (0.2% to 2.0%) and remarked on its increase with better diagnostic aids. The incidence of asynchronous disease reported by other authors is even greater (1% to 14.3%).[17] Obviously the longer the patient survives, the greater the chance of a cancer developing in the second breast. The unadjusted incidence rate for a second breast cancer in our study (6.4/1000 breast-years at risk) was approximately nine times that for a "normal" breast (0.70) and about six times that reported by Ryan and associates[17] in 1958.

McCredie and coworkers[13] recorded a lower age at the time of presentation of patients with asynchronous cancer (in our study the comparison and asynchronous disease groups were younger than the group with synchronous disease). Like us, they also reported a better survival for the asynchronous group but only in women aged less than 50 years at the time of the first diagnosis. In our series the opposite was true: 31% of the women with asynchronous disease were aged less than 50 years; at the end of the study 27% of them were dead or had metastatic disease, compared with only 10% of the 69% of women aged 50 years or more. Al Jurf and colleagues[18] reported a better survival for patients with asynchronous disease at 5 and 10 years (presumably from the date of diagnosis of the first cancer, although this was not stated). McCredie and coworkers[13] predicted in 1975 that with greater use of mammography there should be earlier diagnosis and a better prognosis for bilateral breast cancer. They ascribed the better prognosis of asynchronous cancer to the reduced risk of metastases from the second breast with earlier diagnosis. The better survival of patients with asynchronous disease has been reported by others and ascribed simply to the longer survival necessary for a second cancer to develop.[7] It was disappointing that survival from the date of diagnosis of the second cancer in our series was not better than that for unilateral or synchronous disease even though 53% of the asynchronous second breast cancers were minimal. The apparently later diagnosis of the second breast cancer in eight of the nine patients in whom local recurrence or metastases developed may explain the survival pattern of the asynchronous group when survival was calculated from the date

of the second diagnosis. It is of interest that with the exception of one patient who was lost to follow-up and one patient who died from other causes all the patients with asynchronous *minimal* breast cancer were alive and well up to their last follow-up visit. Only one of them had lymph node involvement (only one node was affected), and she is still well 3 years from the date of the second diagnosis. The M.D. Anderson study compared the survival of patients with either asynchronous or synchronous bilateral breast cancer and that of patients with unilateral disease and found it to be the same in all three groups.[11]

Bilateral breast cancer has been shown to increase the risk of breast cancer in close relatives.[16] However, in a Swedish study no association of familial breast cancer with bilaterality was reported.[19] In our series a family history of breast cancer was not significantly more common in any of the three groups. Our results failed to show the lower age at diagnosis in patients with a family history and bilateral disease described by Al Jurf and colleagues.[18] Radiotherapy in the treatment of cancer of the first breast acting as a possible risk factor for cancer in the second breast was not confirmed in the 20-year M.D. Anderson study,[11] in McCredie and coworkers' study[13] or in our study, although the follow-up period in our study was probably not long enough for proper assessment.

It is difficult to compare our 10-year study of all stage I, II and III breast cancer patients in a total population with the National Surgical Adjuvant Breast Project's 7-year hospital study of stage I and II patients, in which the definition of bilateral disease was "left to the judgment of pathologists and administrators", and synchronous and asynchronous cancers were not separated.[20] That study found that in 25% of the patients, compared with our 37%, the two tumours had the same pathological features. The annual incidence of bilateral disease in that series, 4.2/1000, was less than ours (6.4/1000).

In-situ and invasive lobular carcinoma occurred in similar proportions of each of our groups, contrary to the common belief that such tumours occur more often in bilateral cancer.[21]

Gallagher[22] believes in progression from noninvasive to invasive disease in breast cancer; thus, the presence of more minimal breast cancer reflects earlier diagnosis. The greater incidence of noninvasive cancer, of minimal breast cancer and of cancer detected only by mammography or only by physical examination of the second breast in our series reflects the earlier diagnosis achieved by aggressive screening procedures. In more than 90% of the cases of cancer of the second breast the woman was unaware of any abnormality at the time of the second diagnosis. In contrast, 85% of the women in northern Alberta presenting with unilateral or synchronous bilateral breast cancer discover the lump in one breast themselves, and less than 1% of these tumours are minimal breast cancer.[23] This earlier diagnosis of the second breast cancer emphasizes the need for similar screening for the first breast cancer. Such earlier diagnosis has already been reported from several large screening projects.[24,25] If one believes that minimal breast cancer in the first breast carries a 90% 20-year survival, as suggested by Frazier and coworkers,[26] it may well be worth searching for it in both breasts in asymptomatic women.

Close follow-up of the second breast is indicated for all women with breast cancer. Consideration of prophylactic treatment for the second breast may be necessary in younger women with a family history or lobular or intraduct noninvasive carcinoma in the first breast, and, in view of our findings, with later age at the birth of the first child and a longer interval between menarche and that birth, although this is a very controversial issue. Slack and associates[20] estimated that a routine prophylactic second mastectomy is unnecessary in 98% of patients, whereas Harris and collaborators[27] reported a cumulative risk of cancer of 46.4% for the second breast over 20 years in patients who are premenopausal and have two or more first-degree relatives with breast cancer.

That careful follow-up is essential for the second

breast has been confirmed by our study. Our results reinforce the necessity for awareness by both the patient and the physician of the risk to the second breast[28] and the importance of adequate and aggressive screening of the asymptomatic woman who has never had breast cancer.

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