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Bilateral Breast Cancer

Risk Reduction by Contralateral Biopsy

HAROLD J. WANEBO, M.D., GREGORY M. SENOFSKY, M.D., ROBERT E. FECHNER, M.D., DON KAISER, PH.D., SYLVIA LYNN, R.N., JULIA PARADIES, M.D.

From the Departments of Surgery, Pathology, and Radiology, University of Virginia Medical Center, Charlottesville, Virginia

Although survival from primary breast cancer has improved with earlier diagnosis and treatment, the management of the opposite breast is still in question. The risk factors for bilaterality are known, and preoperative mammography is occasionally helpful, but identification of early second breast cancer is very limited. Contralateral biopsy may provide a reasonable answer to the problem. During a 5-year period, 62 elective contralateral biopsies were performed in patients having mastectomies for primary breast cancer. This consisted of either a mirror image biopsy or, more commonly, a biopsy of the upper outer quadrant. Thirteen patients had simultaneous contralateral cancers, of whom two had clinically overt bilateral cancers and 11 (18%) had clinically occult malignancy. Seven of these 11 had both radiologically and clinically normal breasts. Thus, 11.3% had radiologically and clinically occult cancer demonstrated by biopsy. Surgical management consisted of total mastectomy with low axillary dissection for noninvasive cancers and modified radical mastectomy for invasive cancers. Pathologic findings of the dominant breast cancer and the contralateral lesion were: bilateral, noninvasive: three patients; invasive, noninvasive: (seven patients), and invasive, invasive: three patients. Although follow-up is short (median of 40 months), 82% of the patients who had clinically occult second-breast cancer remain free of disease. During a previous 8-year period, 37 of 500 primary breast cancer patients (7.4%) developed metachronous (33) or synchronous (4) second-breast primary cancers primarily diagnosed clinically or radiologically. Of these, 35 were invasive and two noninvasive cancers; 41% had nodal metastases. A selected "favorable group," 28 of these patients who were free of disease 3 years after their first cancer, was analyzed. The analysis showed that only 10 (36%) were surviving free of disease at 7 years; 25% were free of disease at 10 years. Although the incidence of clinically-recognized, second-primary breast cancer is relatively low, development of a second invasive cancer severely impairs patient survival. Contralateral *biopsy* would appear useful to identify patients with early invasive or preinvasive cancer in the second breast, which appears normal after clinical observation or mammography. It provides opportunity to reduce the risk of invasive cancer in that breast, as well as to provide important diagnostic and prognostic information.

ALTHOUGH SURVIVAL of patients having breast cancer may be improving with the emphasis on early diagnosis and treatment, the management of the opposite breast is still in question. The presence of a pre-existing cancer is stated to be the single most significant determinant for increased risk in the opposite breast. The overall risk for contralateral breast cancer varies depending on the tissue type of the primary cancer as well as on selected host factors. The reported frequency varies from 2 to 14%, with about 34% being synchronous and 66% being metachronous. The annual risk of cancer in the second breast is about 0.65% per year.[1-4] The incidence of a second primary cancer as detected by mammography is in the two to four per cent range.[5-7]

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Reprint requests: Harold J. Wanebo, M.D.; Department of Surgery, University of Virginia, Charlottesville, VA 22908.

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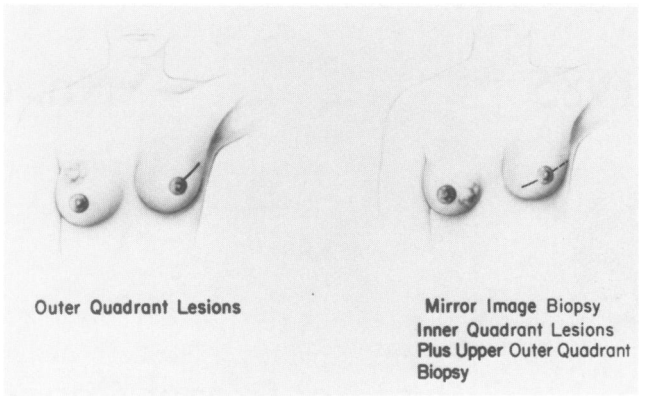

FIG. 1. For outer quadrant lesions, a contralateral biopsy in that quadrant is done. Inner quadrant lesions are biopsied by mirror image and an outer quadrant biopsy.

Although the risk factors for bilateral breast cancer are known and the preoperative mammogram is helpful, detection of early breast cancer in the opposite breast by noninvasive techniques still eludes our best efforts in most cases. Contralateral biopsy would appear to provide a reasonable answer to the problem.

The work of Urban[8,9] and Leis[10-12] suggests the potential for detection of the second breast cancer at an early and highly curable stage. Others have had the opposite findings and believe that contralateral biopsy is of no value.[13-15] We reviewed a small but prospective series of patients evaluated both clinically and by mammography in whom contralateral biopsy was performed at the time of mastectomy for the dominant breast lesion. We compared this group with a retrospective series of patients with primary breast cancer, a portion of whom developed clinically-appreciated cancer in the second breast. Our study focused on the issues of the incidence and detection of the second breast cancer, its impact on prognosis, and the options for patient management under these circumstances.

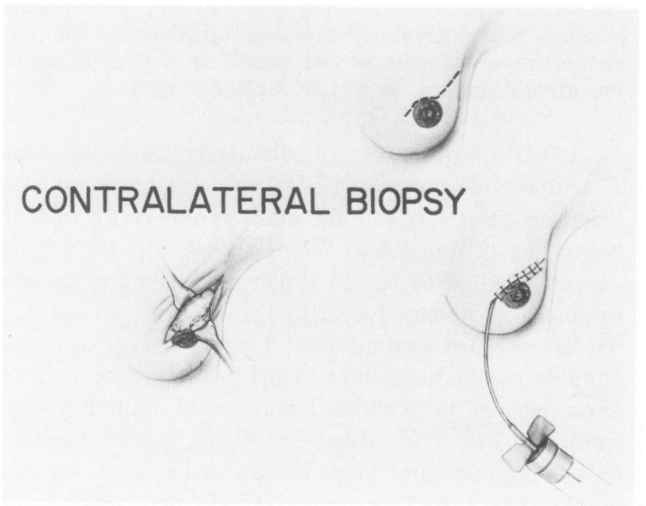

FIG. 2. Contralateral biopsy includes a circumareolar incision with extension to the outer quadrant. This is deepened to breast tissue; 20–25% of breast tissue is excised. A short term suction drain using a Vacutainer tube is employed.

Material and Methods

Patient Selection

During a 5-year period beginning in June 1978, all patients operated on by one surgeon had contralateral breast biopsy as a routine at the time of ipsilateral mastectomy using the general approach of Urban[8,9] (Fig. 1). All patients had mammograms prior to surgery. Special attention was given to the contralateral breast. If significant abnormalities were observed, the planned contralateral biopsy was designed to remove the area in question. On occasion a needle localization was required. In most cases, however, contralateral biopsy was performed in the breast considered normal by physical examination and mammography.

Contralateral Biopsy Technique

The contralateral biopsy was performed with a separate set of instruments. The wound was then closed using a butterfly drain, and the area was covered with sterile dressing (Fig. 2). The ipsilateral breast was then approached with a new instrument set-up and with a change in gloves and gown by the biopsy surgeon.

The general plan was to biopsy the upper outer quadrant of the contralateral breast. If the ipsilateral breast cancer was located in a medial quadrant, an effort was made in selected cases to biopsy the mirror image by extending the incision so as to obtain tissue from the inner quadrant as well. This was not always feasible especially in patients with small breasts, and thus was not a consistent policy. More recently the biopsy has been placed to include the medial segment of the subareolar duct complex because of information suggesting a higher diagnostic rate with that approach.[16]

The biopsy specimen was sent for permanent section, unless an obvious tumor was found; in this case, a frozen section was done for the purpose of obtaining estrogen receptors. Most commonly the biopsy removed about 20 to 25% of breast tissue.

Besides location, the details of the biopsy included placing the incision so that it was cosmetically acceptable (generally within the bra line) and adaptable to performance of a subsequent mastectomy if that were required. The skin incision was carried through the subcutaneous fat to breast tissue *per se* and a "thick flap of skin and fat" was peeled back from the breast to allow removal of breast tissue only (Fig. 2). Careful hemostasis was obtained with electrocautery. The cavity within the

TABLE 1. *Results of Contralateral Biopsy*

Contralateral cancer	13 Patients (21%); median age: 62 yrs (29–67)
Clinically occult	11
Clinically palpable	2
Normal biopsy results	49 Patients (79%); median age: 51 yrs (29–87)
Total	62 Patients

breast was either closed by approximating the cut edges of the breast tissue with two or three carefully placed 5-0 dexon sutures or left open to permit filling in with fluid. To provide short-term closed suction of blood, a number 18 butterfly drain was placed and attached to a vacutainer tube. This was removed within 2 to 4 hours if absolutely dry; if bloody fluid was obtained, it was removed the next day.

Pathology

The dominant breast cancers were classified according to broadly accepted histologic categories.[17,18] For purposes of this study, they have been simply classified as invasive duct or invasive, lobular carcinoma, or noninvasive cancers (intraductal or lobular carcinoma *in situ*).

The tissue from the contralateral biopsy was generously sampled for microscopic examination. As a rule, if the biopsy could be encompassed with 10 blocks or less, it was entirely sectioned. Larger biopsies were sampled with 10 to 25 blocks. If the biopsy had been directed by mammography, specimen radiography was performed. The complete area in question was always submitted for microscopic examination; samples from elsewhere in the biopsy specimen were also submitted. If the mammogram showed areas of calcification, these were confirmed by specimen radiography and verified microscopically.

The diagnosis of lobular carcinoma *in situ* was made based on the criteria of Rosen et al.[19–21] For intraductal cancer, the criteria of Azzopardi were used.[17] All of the diagnoses were confirmed by one of us (REF), who has a special interest in the pathology of breast diseases.

Statistical Analysis

The data were entered on the University of Virginia's mainframe computer. Conventional statistical analysis was carried out using parametric and nonparametric tests. Survival curves were constructed according to the Kaplan Meier method[22] and the differences were compared by the Gehan Wilcoxon test, or by the Cox-Mantel Method.[42]

Results

There were 62 patients with primary breast cancer who had a contralateral biopsy. Almost all had a previous mammogram prior to definitive surgery and the contralateral biopsy. Thirteen (21%) were found to have cancer in the second breast (Table 1). Eleven of these patients had no palpable lesions in the opposite breast. In 49 patients, the results of the biopsy were normal. The median age in the group whose biopsy results were positive was 62; in those patients whose biopsy results were normal, the median age was 51. The mammograms in the patients with clinically-obscure contralateral breast cancer were normal in seven and suspicious in four (Table 2). The two patients with palpable masses in the breast had separate readings of "suspicious" and "negative." In the patients with negative contralateral biopsy results, five had a palpable mass or thickening in the contralateral breast but with normal mammograms. Among the clinically-obscure group, three patients had suspicious/positive mammograms. Thus, there were eight of 41 evaluable patients who had false-positive radiologic or clinical signs of breast disease (Table 3).

TABLE 2. *Synchronous Bilateral Cancer Detected by Contalateral Biopsy: Clinical-Radiologic Findings in Second Breast*

	Normal Mammogram	Suspicious Mammogram
Clinically occult, nonpalpable	7	4
Clinically overt, palpable	1	1

Pathology

Among the 62 patients in the contralateral biopsy group, 49 had normal results from contralateral biopsies. The primary cancer was invasive in 42, and preinvasive in seven (Table 4). Among 13 patients with positive contralateral biopsy results, the primary cancer was invasive in 10 and noninvasive in three. Three patients had bilateral *in situ* cancer, seven had primary invasive and secondary noninvasive cancer, and three patients had bilateral invasive cancer (Table 5). Among the 13 contralateral biopsies, there were six with lobular carcinoma *in situ,* four with intraductal cancer, and three with invasive cancer. The stages of the primary and secondary cancers are shown in Table 6.

Treatment and Follow-up

In 62 patients, the standard of treatment for invasive cancer was modified radical mastectomy; for patients

TABLE 3. *Patients with Normal Contralateral Biopsy Results*

	Clinical Exam	Results of Mammography	
		Suspicious	Normal
Palpable lesion	5	0	5
Nonpalpable	36	3	33
Nonevaluable	8	—	—

TABLE 4. *Synchronous Bilateral Breast Cancer Detected by Contralateral Biopsy*

Ipsilateral Breast	Contralateral Breast	Patients
In situ cancer Stage 0 (3) (LCIS)	*In situ* cancer stage (0) (3) (LCIS)	3
Invasive cancer stage I (2) stage II (3) stage III (2)	*In situ* cancer stage 0 (7) LCIS—3 intraductal—4	7
Invasive cancer stage III (3)	Invasive cancer stage I (1) stage II (1) stage III (1)	3

TABLE 6. *Bilateral Breast Cancer Contralateral Biopsy Series*

	Stage			
	0	I	II	III
Clinically occult group (11)*				
First cancer	3	2	3	3
Second group	5	6	—	—
Palpable disease group (2)†				
First cancer	—	—	—	2
Second group	—	—	1	1

* Nine patients showed no evidence of disease after a median of 40 months (1 to 7 years) follow-up. One patient died of disease at 23 months; one is living with disease after 24 months.

† Both patients died of disease at 11 months.

with noninvasive cancer total mastectomy with low axillary dissection was the standard. Frequently, the management of the second breast coincided with a planned reconstruction of the dominant breast if this was deemed appropriate in the favorably staged patient. The second breast was then primarily reconstructed with a subpectoralis implant. In the group of 49 patients who had normal biopsy results, the survival and recurrence figures are noted in Table 7. Two patients were found to have subsequent cancer in the contralateral breast. One patient, who had a negative contralateral biopsy, but was at high risk by virtue of family history and presence of lobular carcinoma *in situ* in the primary breast, had a total mastectomy prior to mammoplasty of that breast in conjunction with reconstruction and was found to have lobular carcinoma *in situ* in that breast. A second patient, in whom the contralateral biopsy was negative, developed an invasive cancer (Stage III) 3 years later and subsequently died from this. Another patient developed a lesion in the contralateral breast that was determined to be a metastasis. This coincided with development of disseminated metastases.

The overall disease-free survival rate in the patients with negative contralateral biopsy was 76% at a median follow-up of 40 months (Table 7). The relapse free survival rate in the 11 patients with a clinically occult second breast cancer was 82% (median 40 months) (Table 6). Two patients developed recurrence, one of whom died.

TABLE 5. *Contralateral Biopsy Series: Relation to Primary Cancer Type*

Primary Breast Cancer	Contralateral Biopsy		
		Normal	Positive
Noninvasive	10	7	3
Intraductal	3	3	0
LCIS	7	4	3
Invasive	52	42	10
Lobular	5	4	1
Ductal	47	38	9
Total	62	49	13

Bilateral Breast Cancer Clinical Follow-up Series

In a consecutive series of 500 patients observed from 1969 to 1975, 37 (7.4%) had bilateral cancer. Four patients were synchronous and 33 metachronous. The interval between the first and second cancer occurred at a median of 39 months and mean of 77.5 months. The stage of the second cancer is shown in Table 8. The majority were invasive cancer. One-half were Stage I, one-third were Stages II and III, and 14% were Stage IV. In contrast, 77% of the second breast cancers in the contralateral biopsy group were noninvasive (Stage 0).

Effect of the Second Breast Cancer on Survival

In the series of 500 patients who were observed from 1969 to 1975, 100 consecutive patients were selected who survived the immediate hospitalization surrounding the treatment of their primary breast cancer, and who did not develop carcinoma in the second breast. The

TABLE 7. *Follow-up* of 49 Patients with Negative Contralateral Biopsy*

Stage	Patients†	No Evidence of Disease	Recurrence‡	Dead of Disease	Living with Disease
0	8	8	0	0	0
I	10	10	0	0	0
II	14	10	4	1	3
III	9	4	5	4	1
IV	1		1	1	
Unknown	3	3	0	0	0
Totals	46	35 (76%)	10	6	4

* Median follow-up: 40 months (1 to 7 yr).

† Three not staged; three lost to follow-up.

‡ Two developed subsequent contralateral cancer.

TABLE 8. *Detection of Bilateral Breast Cancer: Second Breast Cancer*

	Contralateral Biopsy	Clinical Follow-up
Patients	13 of 62 (21%)	37 of 500 (7.4%)
Mean age	62	60
Type		
In situ cancer	10	4
Invasive cancer	3	33
Stage		
0	10	2
I	1	18
II	1	4
III	1	8
IV	0	5

probability of disease-free survival in these patients (all stages) was 68% at 5 years and 54% at 10 years (overall survival was 69% and 56%, respectively) (Table 9). In comparison, the disease-free survival after the first diagnosis in the 37 patients who subsequently developed carcinoma in the second breast was 89% at 5 years (significantly better than the unilateral group) and 63% at 10 years (not different from unilateral breast cancer group). If one compares the survival after the first diagnosis, in patients who were Stages I and II there were no survival differences at 5 years, and at 10 years there was a suggested (but not significant) trend in favor of the patients who developed unilateral cancer only (Table 9). The disease-free survival determined from diagnosis of the second breast cancer was 61% at 5 years and 23% at 10 years. If we select a "favorable group" of patients who had greater than a 36-month interval between the detection of the first and second breast cancer, there were 28 such patients (77%) who were free of disease regarding their first breast cancer at time of detection of the second cancer. Eighteen of these patients had serious complications of their cancer. Five of these patients presented with Stage IV disease in the second breast and 14 developed subsequent recurrence at a median follow-up of 7 years. Only 36% of this group were free of disease at 7 years and 25% at 10 years.

Because of small numbers and short follow-up, these patients cannot be statistically compared with the 11 patients in the contralateral biopsy series. At a median follow-up of 40 months, 9 of the 11 (82%) are free of disease. Of the 46 patients with negative contralateral biopsies who had adequate follow-up, 76% are disease-free at the same interval.

Discussion

The true incidence of clinically apparent bilateral breast cancer varies pending on the methods of study, the type of population, and the length of the period of observation. The overall incidence in a collected series was 3.7% with a range of 1.8% to 8.6% (Table 10).[3,23-34] The majority of these (72%) were metachronous

TABLE 9. *Comparison of Disease-free Survival (DFS)* in 37 Bilateral Breast Cancer Patients with that of 100 Patients Who Had Unilateral Cancer Only†*

	Years after First Breast Cancer						
	1	2	3	4	5	7	10
Total group (all stages)							
Bilateral cancer							
Patients (37)	37	35	—‡	—	34	30	17
DFS	0.97	0.92	—	—	0.89	0.78	0.63
Unilateral cancer							
Patients (100)	97	87	71	71	68	64	45
DFS	0.96	0.88	0.81	0.71	0.68	0.64	0.54
Difference (P)				0.009	0.006	0.06	0.09
Stage I/II (first cancer)							
Bilateral cancer							
Patients (17)	17	17	—	—	16	15	8
DFS	1.0	0.94	—	—	0.88	0.82	0.60
Unilateral cancer							
Patients (66)	64	62	61	54	51	49	43
DFS	0.98	0.94	0.92	0.82	0.77	0.74	0.69
Difference (P)				0.15	0.08	0.24	0.43
	Disease-free Survival after Second Breast Cancer						
Bilateral cancer							
Patients	33	31	29	22	21	17	15
DFS	0.94	0.89	0.83	0.64	0.61	0.54	0.23

* Derived from Kaplan Meier Survival Curve Plot.

† Derived from 500 consecutive breast cancer patients seen from 1969 to 1975.

‡ Missing data points are "non-events" in plot. Differences are calculated by Cox Mantel method.

TABLE 10. *Occurrence of Bilateral Breast Cancer*

Author	Bilateral Cancer/ Total Patients	Synchronous Cancer Patients	Metachronous Patients	Interval Between First and Second Cancer
Al-Jurf (Univ. of Iowa, 1981)	104/5608	26	78	123 Months
P. Burns (Alberta, UK, 1981)	66/1351	3	63	10 years
S. Schell (M.D. Anderson, 1981)	106/2231	48	58	7 months to 10 years
Stage I/II Br Ca Bailey (St. George, England, 1980)	39/911	17	22	5 years, 8 months
J. Buls (Melbourne, 1976)	76/NS	21	55	Majority, 5 years
H. Kesseler* (NYU/Columbia, 1976)	35/967	17	18	Unknown
E. Lewison (Johns Hopkins, 1971)	42/490	8	34	6 Years
C. McLaughlin (Univ. Nebraska)	38/475	NS†	NS	Majority, 5 years
N. Slack (Nat. Surg. Adj.) Stage I/II Br Ca	52/2734	0	52	1 to 67 months
J. Hermann (NYMC, 1973)	31/418	3	28	6.3 years
J. Devitt* (Ottawa, 1970)	28/1530	17	11	NS
J. Farrow (Memorial NY, 1957)	202/5576	21	18	5 to 10 years
T. Hubbard* (Minnesota, 1952)	17/272	0	17	Majority, 5 years
Total	836/22563 (3.7%)	81 (29%)	454 (71%)	

* Quoted in references 1, 3, and 12.

† NS = Not stated.

cancers. Perhaps the detailed study by Robins and Berg is closest to the mark.[1] They observed a cumulative incidence of 3.8% at 5 years, 6.8% at 10 years, 9.5% at 15 years, 12.8% at 20 years, and 16.4% at 30 years (as updated by Adair).[2] The annual risk for developing cancer in the second breast was at an average rate of 0.67% per year. The overall risk for a second cancer was five times that in the general population, 10 times normal for women less than 50 years of age, and two times normal for women over 70. Similar though lower risk factors were noted by Burns[3] and Prior and Waterhouse.[4] High risk factors for developing a second breast carcinoma include: (1) previous history of lobular cancer, or lobular cancer *in situ;* (2) known precancerous mastopathy, atypical lobular, or duct hyperplasia; (3) close family history of breast cancer, especially if premenopausal or bilateral; and (3) the potential for long-term survival from the first cancer (if low stage).[1,3,12,20] In the past, certain authors advocated contralateral mastectomy as a way of reducing the risk of the second cancer, but this was never widely adapted.[10,35,36] Contralateral biopsy seemed a reasonable alternative to this extreme measure.

Contralateral biopsy has been evaluated by several authors, again with varying results ranging from a yield of two per cent in the Mayo Clinic Series (reported by Martin 1981) to 12.5% in the series reported by Urban and the recent report by Fracchia (Table 11).[6,8,10,13–15] Urban has long adopted a routine policy of performing a generous excisional biopsy of the opposite breast at the time of mastectomy for a known breast cancer.[8] The truly occult lesions detected by contralateral biopsy in the absence of definitive x-ray or physical signs were at a much earlier stage of development, the majority being noninfiltrating or *in situ* cancers. Urban found 119 cancers (12.5%) in the second breast out of 954 biopsies. The majority were noninfiltrating cancer (60%); of those infiltrating cancers, only 8.5% had positive axillary nodes, usually of a minimal degree. This is in contrast to the findings when the second breast cancer was demonstrated by physical examination or by mammography; in this case, most were infiltrating cancers, and 45% had positive nodes. His technique was to excise approximately 25% of the breast parenchyma, removing a fusiform piece of glandular tissue. When no specific physical or x-ray findings were present, Urban excised the tail of the breast and the mirror image of the known primary through one incision if possible. When no physical or x-ray signs were found, carcinoma was found in eight per cent; 60% of these were *in situ* or noninvasive cancers. The overall incidence of simultaneous contralateral cancer was 12.5% if the dominant cancer was invasive, and 19% if the dominant cancer was noninvasive. Mammography was negative in two-thirds of the

TABLE 11. *Diagnosis of Second Breast Cancer by Contralateral Biopsy*

Author	Year (Reference)	Incidence of Positive Biopsies (%)
Fracchia, A.	1985 (39)	12.7
Urban, J. A.	1967–1977 (8, 9)	12.5
Leis, H. P.	1978 (10)	7.59
Fenig, J.	1975 (6)	7.3
Andersen, L. I.	1980 (13)	5.9
King, R. E.	1978 (14)	4.5
Martin, J. K.	1981 (15)	2.0

bilateral breast cancer patients examined. Urban's overall rate of bilateralism (including asynchronous cancers) was 15.7%. The patients having negative contralateral biopsy had a low incidence (two per cent) of later developing cancer in the contralateral breast. In Urban's own series of patients treated with extended radical mastectomy, the incidence of clinically-detected, second-breast cancer was 10% in the overall group and 15% among those surviving 10 years.[9]

Leis has obtained similar data in a series of 321 random biopsies of the opposite breast in 500 breast cancer patients.[10-12] Occult primary cancer was found in 7.5%, and atypia was present in 15.3%. Of these cancers, 41.7% were invasive, and 58% were noninvasive. Overall, 22.7% had either atypia or cancer.[22,23] This overall figure is similar to Urban's overall figure (atypia and cancer) of 22.4%.[9] A major difference in these two series and possibly in our own is the interpretation and designation of the preinvasive lesion (or the precursor lesion).

A recent report by Fracchia et al. described 403 patients with bilateral breast cancer.[34] This represented an incidence of 12.7% in breast cancer patients seen during a 10-year period; of these, 44% were synchronous and 56% metachronous. The presence of bilateral breast cancer was considered to place the patients in double jeopardy. The 10-year-relapse-free survival rate for bilateral, Stage I breast cancer was 71.4%. When size was not considered, survival rate was 57.1%—significantly worse than for invasive breast cancer without nodal involvement. The presence of noninvasive cancer in the second breast, if properly treated, was thought not to impair the survival. The highest disease-free-survival occurred in patients with bilateral *in situ* cancer (98% at ten years), followed by the combination of invasive and *in situ* (75%), and bilateral invasive (51%). Fracchia made a plea for random biopsy of the opposite breast, particularly the upper outer quadrant with inclusion of the subareolar area. This latter point in technique appeared to have enhanced the diagnostic rate.

Conclusion

Our series, though very small, has essentially confirmed the data from the Memorial Hospital series. We found contralateral cancer by biopsy in 11 patients (18%) with clinically occult lesions. Seven of these (11%) were truly occult lesions both radiologically and by physical examination. If we count only these, our incidence of radiological- and clinically-occult cancers is 11%. These numbers are essentially similar to those reported by the Memorial group but are much higher than those reported by the Medical College of Virginia and the Mayo Clinic.[14,15] This is considered to be a function of more extensive sampling in our cases. Patchefsky et al. have shown objectively what may appear obvious, namely that an increased number of sections will result in an increased frequency of finding noninvasive cancer.[37] Although it is recognized that there is subjectiveness in the diagnosis of noninvasive carcinoma, the pathologist in our study considers himself to be conservative and to adhere to rigid criteria as objectively as possible with a high rate of reproducibility. In some centers, the term lobular carcinoma *in situ* is never used and is replaced by lobular neoplasia.[38] It is of interest that the final outcome, whether called lobular carcinoma *in situ* or lobular neoplasia is very similar. About 22% of these patients will develop invasive cancer in that breast and will have a similar incidence in the contralateral breast if observed over twenty years (Haggensen et al. and Rosen et al.).[19,20,38]

The question of management of the *in situ* lesion is controversial, and diametrically opposed views prevail. Some suggest total mastectomy[21] and others observation only.[38] There is less controversy about the intraductal cancer as these have a high frequency of microinvasive cancer if searched for. Moreover, about 45% or more have multifocal cancer. If untreated, over 28 to 50% will progress to invasive cancer capable of metastasizing.[20,39]

In our clinically observed series, 7.4% developed contralateral cancer at a median of 3.5 years after treatment of the first breast cancer. About 90% of these were invasive, and most were metachronous cancers. One-third had Stage III and IV lesions. If one measured the survival from time of first diagnosis, the survival of the overall bilateral breast cancer group appeared better than that of the patients who had unilateral cancer only. This probably represented a staging imbalance, because if one compared patients whose first cancer was Stage I or II only, there were no survival differences. The survival as measured from time of the second diagnosis, however, was distinctly poor in the bilateral breast cancer patients (61% survived disease-free at 5 years and 23% at 10 years). Even if one analyzed survival of a selected favorable group of second breast cancer patients, only 36% were surviving free of disease at a median of 7 years. The latter included only patients who were free of disease from their first breast cancer over 3 years from time of diagnosis of the second breast cancer.

Our data suggest that the second breast cancer places the patient in double jeopardy, as stated by others. Of the numerous series reported, there have been differences in the effect of the second breast cancer on survival. Some authors have reported that the second breast cancer is usually smaller and at an earlier stage and the patient may even have benefited immunologically by exposure to the first breast cancer.[25,29] This latter point

has been questioned by others, however.[40] If one measures survival from time of development of the first cancer, there is also the paradox of apparent better survival in some series of patients who developed second breast cancer compared to their counterparts who had unilateral cancer. This benefit may be more apparent than real as shown by the detailed analyses by Robbins and Berg.[1] Patients who develop metachronous breast cancer (the majority of the patients) have already survived the high risk 2- to 3-year period which affects patients who develop recurrence of their primary cancer. If one controls for this as Robbins and Berg have done, then it can be shown that patients who develop the second lesion have a much higher death rate than their matched controls in the year immediately following development of the second cancer, as well as having a continued higher death rate. Beyond 20 years, the risk of death from the second breast cancer is 21% compared to four per cent for the first cancer. This is disputed by others however.[25,28,29] In general, the occurrence of a second invasive cancer (even if low stage) is an added detriment and, as noted by Robbins and Berg, the occurrence of a second breast cancer acting in conjunction with the first cancer almost halved the expected survival of the patient.[1]

In conclusion, the data presented here suggest that contralateral breast cancer can be diagnosed in the clinically and radiologically normal breast at its earliest stage by contralateral biopsy (primarily of the upper outer quadrant and subareolar area). The carcinoma thus diagnosed is commonly preinvasive, and in three-quarters will be lobular cancer *in situ*. This early recognition should permit management decisions based on the data. If reconstruction of the dominant side is planned, then perhaps total mastectomy of the contralateral breast is in order with immediate reconstruction using a subpectoralis implant or a tissue expander. The nipple areolar complex (if intraductal cancer) is at increased risk for involvement (over 20% according to Lagios et al.[41]) and should be removed with the total mastectomy. Lobular carcinoma *in situ* could be managed the same way, with consideration perhaps of retaining the nipple areolar complex in which a 'shave' biopsy of the base has been done. Nipple reconstruction has been highly improved in recent years and this may be a moot point. If close observation is employed as the management technique for lobular carcinoma *in situ*, then perhaps a more aggressive and long-term follow-up program should be adopted for the second breast with the need to continue observation well beyond twenty years. Frequent physical examination, patient self-examination and mammography about twice a year would appear to be a minimum. If the contralateral cancer is invasive, this should be treated in the conventional way either by modified radical mastectomy or segmental resection and axillary dissection and breast irradiation if considered appropriate. Contralateral biopsy is best considered as a routine procedure that is most useful in women who have an expected long-term survival from this first cancer and in those with special factors indicating increased risk of bilaterality. The increased risk factors are: (1) a close family history (especially if premenopausal or bilateral); (2) multicentricity or presence of lobular carcinoma *in situ* in the dominant breast lesion; and (3) patients with parenchymal patterns adverse to mammography or dense breasts (P2 or DY) as described by Wolfe, which are difficult to monitor radiographically.[7]

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Discussion

DR. ALFRED S. KETCHAM (Miami, Florida): I was privileged to discuss with Dr. Wanebo, over the telephone, the contents of his presentation, but I am somewhat astounded now that I hear the paper presented and see before me many of his figures and the analytical data.

Our most common cancer killers in women are lung and breast. We know what causes lung cancer, but preventing it interferes with our lifestyle, so the public does little or nothing about it. Breast cancer—we know nothing about its cause, so both of these lesions lead us to the mandate for early recognition, and an attempt at early recognition is the essence of this paper.

Although the Fisher National Surgical Adjuvant Breast Project (NSABP) study is not yet published, we hear rumors that there is an alarmingly high recurrence rate in the segmental mastectomy patients that did not receive postoperative radiation therapy. I understand that it is a local recurrence rate and not a new cancer or a manifestation of multiple primary disease. If this is local recurrence, then in my judgment, the surgery was not totally encompassing of the primary tumor. There is no other explanation for a recurrence rate of 10 to 20%, or whatever it will be shown to be.

The real question we would like to have an answer for is "What is the multiple primary identification rate for invasive tumors, occult or not, in these segmental and total mastectomy specimens and, very importantly, in the residual breast following partial mastectomy as well as in the opposite breast as identified by long-term follow-up? How alarmingly high is the incidence of cancer complication in the so-called normal breast tissue?

Dr. Wanebo gives us an astounding high rate of 26%. We believe that is somewhat higher than what the long-awaited NSABP B-06 three-armed study will show. A critical factor will be when these figures are differentiated for us as to whether we are dealing with invasive cancer or whether it will break down to about 90% noninvasive incidence in the contralateral breast, as compared to less than 10% of truly invasive cancer.

Are noninvasive cancers, intraductal cancers, carcinomas *in situ,* or even lobular carcinomas *in situ* really precursors of subsequent infiltration? This has never been unequivocally shown in the breast or, I believe, in the cervix, although Rosen and others certainly worry us with their reports. If it is true, and if Dr. Wanebo's figures hold up for the contralateral breast, then not only is contralateral biopsy indicated, but possibly more aggressive surgery than just biopsy might be considered on the opposite side.

The second part of Wanebo's studies demonstrate a seven per cent second primary in the opposite breast. In these cancer-aware patients, who supposedly are looking for early recognition signs, 41% had positive nodes; 59% developed distant metastases. These are not only astounding figures, but very, very alarming.

I routinely perform a contralateral biopsy with a 3-mm stab wound in the para-areolar complex and then use the pituitary biopsy forceps to remove six to eight small specimens per breast. Our incidence is approximately eight per cent for contralateral abnormalities, of which only one per cent are shown to be truly invasive.

Dr. Wanebo, your figures suggest we should more often consider the possibility of performing prophylactic mastectomy. Is that what you would like us to consider?

What is the incidence of invasive cancer found in your total mastectomy specimens, occult or otherwise? On occasion, you perform segmental mastectomy with breast preservation and cosmetic acceptance. Is this for invasive cancers? However, your figures suggest, and you have been heard to say, that we might consider prophylactic mastectomy for noninvasive cancer. Harry, how can you consider doing a total mastectomy for something that has never been proven to be cancer,