A Comparison of Bilateral Breast Cancers in *BRCA* Carriers

Jeffrey N. Weitzel,[1] Mark Robson,[2] Barbara Pasini,[3] Siranoush Manoukian,[3] Dominique Stoppa-Lyonnet,[4] Henry T. Lynch,[5] Jane McLennan,[6] William D. Foulkes,[7] Teresa Wagner,[8] Nadine Tung,[9] Parviz Ghadirian,[10] Olufunmilayo Olopade,[11] Claudine Isaacs,[12] Charmaine Kim-Sing,[13] Pal Møller,[14] Susan L. Neuhausen,[15] Kelly Metcalfe,[16] Ping Sun,[16] and Steven A. Narod[16]

[1]Department of Clinical Cancer Genetics, City of Hope Cancer Center, Duarte, California; [2]Department of Human Genetics and Medicine, Memorial-Sloan Kettering Cancer Center, New York, New York; [3]Istituto Nazionale Tumori, Milan, Italy; [4]Institut Curie, Paris, France; [5]Department of Preventive Medicine and Public Health, Creighton University School of Medicine, Omaha, Nebraska; [6]San Francisco Comprehensive Cancer Center, University of California, California; [7]Department of Medicine, Division of Medical Genetics and Department of Human Genetics, McGill University, Montreal, Quebec, Canada; [8]Department of Obstetrics and Gynecology, University of Vienna, Austria; [9]Beth Israel Deaconess Medical Center, Boston, Massachusetts; [10]Epidemiology Research Unit, Hôtel-Dieu de Montréal, Canada; [11]Center for Clinical Cancer Genetics, University of Chicago, Illinois; [12]Lombardi Cancer Center, Georgetown University Medical Center, Washington, DC; [13]British Columbia Cancer Agency, Vancouver, British Columbia, Canada; [14]Unit of Medical Genetic Counselling, Department of Cancer Genetics, The Norwegian Radium Hospital, Oslo, Norway; [15]Division of Epidemiology, Department of Medicine, University of California, Irvine, California; and [16]The Centre for Research in Women's Health, University of Toronto, Ontario, Canada

Abstract

Background: **Women with breast cancer and a *BRCA* mutation have a high risk of developing a contralateral breast cancer. It is generally believed that the two cancers represent independent events. However, the extent of concordance between the first and second tumors with respect to hormone receptor expression and other pathologic features is unknown.**

Purpose: **To determine the degree of concordance of estrogen receptor (ER) status, tumor grade, and histology in tumors from women with bilateral breast cancer and a *BRCA* mutation.**

Subjects and Methods: **Women with a history of bilateral invasive breast cancers were selected from an international registry of women with *BRCA1* or *BRCA2* mutations. Medical records were reviewed to document the characteristics of each cancer and the treatments received.**

Results: **Data were available for 286 women with bilateral breast cancer and a *BRCA* mutation (211 *BRCA1*; 75 *BRCA2*). The mean interval between first and second tumor was 5.1 years. The two tumors were concordant more often than expected for ER status ($P < 0.0001$) and for grade ($P < 0.0001$), but not for histology ($P = 0.55$). The ER status of the first tumor was highly predictive of the ER status of the second tumor (odds ratio, 8.7; 95% confidence interval, 3.5-21.5; $P < 0.0001$). Neither age, menopausal status, oophorectomy nor tamoxifen use was predictive of the ER status of the second tumor.**

Conclusions: **There is strong concordance in ER status and tumor grade between independent primary breast tumors in women with a *BRCA* mutation. The excess concordance may be due to common risk factors, genetic variation, or the existence of a preneoplastic lesion that is common to both tumors.** (Cancer Epidemiol Biomarkers Prev 2005;14(6):1534–8)

Introduction

Mutations in the genes for hereditary breast and ovarian cancer, *BRCA1* and *BRCA2*, confer a lifetime risk of breast cancer of 56% to 87% (1, 2). After an initial diagnosis of breast cancer, the risk for a contralateral second primary breast cancer in a *BRCA* carrier is ~3% per year, or 30% at 10 years postdiagnosis (3, 4). It has been assumed that the second primary breast cancer represents a new event, and is independent of the first breast cancer (5). We recently observed that the risk of breast cancer in *BRCA1* carriers was increased 1.7 times if the contralateral breast was previously affected—that is, having a diagnosis of breast cancer in one breast increases the chances that the other breast will be affected at a later date.[17] This observation leads us to question the assumption of the independence of the two breast cancers in women who develop bilateral breast cancer. The two breast cancers may not truly be independent in women who develop bilateral breast cancer, but rather associated with common genetic or environmental risk factors, or the existence of a preneoplastic lesion that is common to both tumors.

In the case of nonhereditary bilateral breast cancer, there is often concordance beyond the expected degree in the hormone receptor status of the two cancers (6-11). In general, the degree of concordance is greater for tumors that present simultaneously (synchronous breast cancers) than for cancers which present at different times (asynchronous breast cancers; ref. 12). In a recent study of bilateral breast cancer cases in National Surgical and Adjuvant Breast and Bowel Project trials, the estrogen receptor (ER) status of the initial breast cancer was strongly associated with that of the contralateral breast for patients who did not receive tamoxifen [odds ratio (OR), 14.8; 95% confidence interval (CI), 3.8-74.3], but not for patients who received tamoxifen (OR, 3.4; 95% CI, 0.53-39.2; ref. 11). The extent of concordance between the first and second primary tumors with respect to hormone receptor expression (or other factors) is currently unknown for women

Received 1/26/05; revised 3/22/05; accepted 4/7/05.

Grant support: Canadian Breast Cancer Research Alliance and the California Cancer Research Program of the University of California, grant number 99-86874 (to J.N. Weitzel), NIH CA74415 (to S.L. Neuhausen), and NIH EDRN grant 1 UO1 CA86389 (to H. Lynch).

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Requests for reprints: Steven A. Narod, The Centre for Research in Women's Health, 790 Bay Street, Toronto, Ontario, Canada M5G 1N8. Phone: 416-351-3765; Fax: 416-351-3767. E-mail steven.narod@sw.ca

[17] Submitted for publication.

with *BRCA* mutations. These findings may have implications for our understanding of the origin of hereditary breast cancer, and may be informative for developing intervention strategies.

Materials and Methods

Women with bilateral breast cancer were identified through a registry of *BRCA1* and *BRCA2* carriers located at the University of Toronto. All carriers have deleterious *BRCA* mutations (women with unclassified variants are not included). Participating centers were requested to submit data to the study center on the characteristics of these tumors; specifically, on ER status (positive, negative, equivocal, not done), on grade (1, 2, 3, missing) and on histology (ductal, medullary, lobular, other, unknown). Data on stage were not available. These data were collected by review of medical records (clinical notes and/or pathology reports) at the individual centers. There were different clinical standards for determining ER status at different centers; most had been determined by direct measurement in cytosol or by immunohistochemistry. Reports indicating weakly positive staining were classified as equivocal. Pathology reports with a description of well, moderately, or poorly differentiated histology were assigned to grades 1, 2 and 3, respectively. Cancers reported to be of mixed grade were assigned to the higher category. Histologic subtype was determined by the dominant component if there was mixed histology, and classified as ''other'' if designated as adenocarcinoma, not otherwise specified. Cases of ductal carcinoma *in situ* or lobular carcinoma *in situ* without an invasive component were excluded. Four women carried mutations in both *BRCA1* and *BRCA2* and were excluded. Women who had evidence of metastatic disease at, or prior to, the diagnosis of the contralateral breast cancer were also excluded.

A total of 31 centers responded to the request to provide data and reported a total of 517 cases of bilateral cancer; 286 cases (55%), for whom data was available on ER status and/or histologic grade for both tumors, were eligible for the study.

Statistical Analyses. The two tumors were compared for concordance for ER, histology, and grade using χ^2 analyses. ORs were estimated for the odds of the second tumor being ER-positive, conditional on the ER status of the first tumor. Women who had ER status assigned as equivocal were excluded from these comparisons. Grade was assigned to three categories. ORs for grade were constructed by comparing those with grade 1 tumors to those with grade 2 or 3 tumors, and by comparing those with grade 1 or 2 tumors with those with grade 3 tumors. Multiple logistic regression was done to determine which variables were predictive of the ER status of the second tumors. SAS 8.2 was used for all analyses.

Results

Data was available for 286 women with a history of bilateral breast cancers (Table 1). There were 211 women with *BRCA1* mutations and 75 women with *BRCA2* mutations. For 45 women, the tumors presented synchronously (within the same calendar year), and for 241 women, the tumors presented in different years (asynchronously). The mean age of diagnosis of the first breast cancer was 38.6 years for *BRCA1* carriers and was 43.6 years for *BRCA2* carriers ($P < 0.0001$ for difference). The mean interval between the first and second breast cancers was 5.1 years (range 0-23 years) for *BRCA1* carriers and 5.2 years (range 0-18 years) for *BRCA2* carriers. Characteristics of the tumors are presented in Table 2. The majority of the *BRCA1*-associated tumors were ER-negative (82%), whereas the majority of *BRCA2*-associated tumors were ER-positive (79%). Among *BRCA1* carriers, the proportion of ER-positive cancers increased with age of diagnosis (Table 3). No similar trend was present for *BRCA2* carriers.

Table 1. Characteristics of the 286 women with bilateral breast cancer

	BRCA1 (n = 211)	*BRCA2* (n = 75)	*P*
Date of Birth	1951.2	1946.6	0.001
Mean age of first breast cancer	38.6	43.6	<0.0001
Mean age of second breast cancer	43.7	48.6	<0.0001
Mean interval	5.1	5.2	0.92
Oophorectomy (%)			
No	187 (89.0)	62 (83.8)	0.24
Yes	23 (11.0)	12 (16.2)	
Unknown	1	1	
Menopausal status at time of diagnoses (%)			
First pre, second pre	101 (54.9)	21 (31.8)	<0.0001
First pre, second post	49 (26.6)	15 (22.7)	
First post, second post	34 (18.5)	30 (45.5)	
Unknown	27	9	

NOTE: If menopause and breast cancer occurred in the same calendar year, the cancer was classified as premenopausal.

The right and left breast cancers were compared for ER status, for grade, and for histology (Tables 4-6). The expected degree of concordance was calculated by inspection of the two-by-two tables, and the significance of the association was calculated using the χ^2 test. The concordance between first and second primary tumors for ER status was much greater than expected for both *BRCA1* (OR, 6.4; $P < 0.0001$) and for *BRCA2* (OR, 9.5; $P = 0.002$; Table 4). Following an ER-negative breast cancer, 88% of contralateral breast cancers in *BRCA1* carriers were ER-negative. In contrast, following an ER-positive breast cancer, 54% of contralateral cancers in *BRCA1* carriers were ER-negative ($P < 0.0001$ for difference). Following an ER-positive breast cancer in *BRCA2* carriers, 83% of contralateral cancers were ER-positive. Following an ER-negative breast cancer, only 33% of contralateral breast cancers in *BRCA2* carriers were ER-positive ($P = 0.002$).

There was also a greater degree of concordance than expected between bilateral cancers for grade ($P < 0.0001$). For *BRCA1* carriers, the OR for the second tumor to be of grade 1, given a first tumor of grade 1, was 31.1 (95% CI, 7.5-129.2); the OR for the second tumor to be of grade 3, given that the first tumor was of grade 3, was 2.8 (95% CI, 1.20-6.58). Among *BRCA2* carriers, the corresponding ORs were 30.8 (95% CI, 2.6-369.1) and 1.4 (95% CI, 0.41-4.82), respectively.

The majority of cancers were of ductal histology (83.4% for *BRCA1* and 88.6% for *BRCA2*). Overall, 130 bilateral cancers were concordant for histology, compared with 123.7 expected ($P = 0.55$; Table 6). Among *BRCA1* carriers, 10.6% of the breast cancers were of medullary histology; however, among 25 *BRCA1* carriers whose first cancer was medullary, only 4 women (16%) had a contralateral cancer that was also medullary.

Among *BRCA1* carriers, the extent of concordance for ER status was greater for those diagnosed within the same year (86% of 28 concordant) compared with those diagnosed in different years (79% of 108), but the difference was not statistically significant. Among *BRCA2* carriers, all 15 synchronous tumors were concordant for ER status, compared with 73% of 40 asynchronous tumors. The greater extent of concordance for women with a shorter interval between cancers was present for 5 years (Table 7).

To establish if the effect of concordance of ER status might be attributable to age, or to menopausal status, or to previous hormonal treatment, a regression analysis was done to look for factors which predicted the ER status of the second tumor.

Table 2. Clinical features of breast cancers and treatments received for the first breast cancer

	First breast cancer	Second breast cancer
Year of diagnosis (SD)	1989.9 (6.7)	1995.0 (5.8)
Age of diagnosis (SD)	39.9 (8.8)	45.0 (9.8)
Grade # (%)		
1	18 (8.6)	23 (10.7)
2	48 (23.1)	60 (27.9)
3	142 (68.3)	132 (61.4)
Unknown	78	71
ER status (%)		
Negative	163 (66.3)	141 (64.7)
Positive	83 (33.7)	77 (35.3)
Unknown	40	68
Histology (%)		
Ductal	223 (83.2)	221 (87.7)
Medullary	28 (10.4)	15 (5.9)
Lobular	8 (3.0)	7 (2.8)
Other	9 (3.4)	9 (3.6)
Unknown	18	34

Oophorectomy or adjuvant treatment with hormone antagonists (e.g., tamoxifen or aromatase inhibitors) had only a borderline effect on the receptor status of the second tumor. The receptor status of the first tumor was the greatest predictor of the receptor status for the second tumor (OR, 8.7; 95% CI, 3.5-21.5; $P < 0.0001$) and the effect was not modified by adjustment for age or hormonal factors (Table 8). Because menopausal status and prior oophorectomy are strongly colinear, only oophorectomy was entered into the initial model. The regression was then repeated, substituting menopausal status for oophorectomy, and the results were essentially the same (data not shown). There was little difference in the extent of concordance for ER status depending on the menopausal status of the woman at time of cancer; among all carriers, there was 85% concordance for ER status among women for whom both tumors were diagnosed prior to menopause, compared with 74% concordance for all others (Table 9). Tamoxifen use was not associated with ER status in the contralateral tumor among *BRCA1* carriers; the OR for tamoxifen and ER-positivity was 1.44 (95% CI, 0.4-5.4). Among 21 women with *BRCA1* mutations who took tamoxifen, 5 (24%) had ER-positive contralateral breast cancers; among 132 women who did not take tamoxifen, 25 (19%) had ER-positive breast cancers. Among *BRCA2* carriers who took tamoxifen, the OR was 0.26 (95% CI, 0.04-1.6), suggesting a possible effect for *BRCA2* carriers, but the number of subjects in the latter group was small.

Discussion

We observed a strong degree of concordance in both ER status and tumor grade between the right and left breast cancers in women with a *BRCA1* or *BRCA2* mutation. Our results are similar to those reported for the nonhereditary population.

Table 3. Association between age of diagnosis and ER status (first breast cancers only)

Population	Age group	Number of cases	ER+ (%)	P*
BRCA1	≤44	142	15.5	
	45-54	34	23.5	
	≥55	6	66.7	0.005
BRCA2	≤44	36	83.3	
	45-54	17	58.8	
	≥55	11	81.8	0.47

*Cochran-Armitage trend test.

Table 4. Association between ER status of the first and second breast cancers

	First ER−	First ER+	Total
BRCA1			
Second ER−	99	13	112
Second ER+	13	11	24
Total	112	24	136
BRCA2			
Second ER−	6	8	14
Second ER+	3	38	41
Total	9	46	55

NOTE: OR, 6.4; $P < 0.0001$ (χ^2 test) for *BRCA1*. OR, 9.5; $P = 0.002$ (χ^2 test) *BRCA2*.

In the general population, the rate of contralateral breast cancer (about 0.7% per year) seems to be independent of age and is relatively constant for the 20-year period following the first diagnosis (13). Newman et al. reported on 70 bilateral breast cancer cases treated between 1983 and 1994 (9). ER status was the same for 60% of 26 cases where data was available for both. Using retrospective data, available on 110 of 176 bilateral breast cancer cases from the National Surgical and Adjuvant Breast and Bowel Project trials B-18, B-22, and B-25, Swain et al. recently reported that the ER status of the primary breast cancer was associated with that of the contralateral breast for patients not receiving tamoxifen (OR, 14.8; 95% CI, 3.8-74.3), but not for patients with ER-positive tumors who received tamoxifen (OR, 3.4; 95% CI, 0.53-39.2; ref. 11). We did not find that tamoxifen use was associated with an increase in the proportion of ER-negative contralateral breast cancers—this suggests that tamoxifen is equally effective in preventing ER-positive and ER-negative breast cancers, and is consistent with our previous observation that tamoxifen prevented contralateral breast cancer in both *BRCA1* and *BRCA2* carriers (14). We also observed a greater degree of concordance for cancers that were diagnosed within the same year (or within a few years) than for cancers that were separated more widely in time, although our results did not reach statistical significance and the effect was not present for *BRCA2* carriers. In an early study, Kiang et al. reported that 10 of 11 synchronous bilateral breast cancers were concordant for ER status, compared with only two of seven asynchronous tumors (6). Coradini et al. reported on 399 patients with bilateral breast cancer operated on at a single institution over a 20-year period (94 synchronous and 305 asynchronous), noting that the ER levels in the two tumors (treated as a continuous variable) were highly correlated (10). They also reported a greater degree of concordance for synchronous than for asynchronous breast cancers. In our study, there was no clear excess of concordance for tumor histology, but almost all cancers (88%) were ductal. Gogas et al. reported that among 78 bilateral cases, 63% were

Table 5. Association between grade of the first and second cancers

	First grade 1	First grade 2	First grade 3	Total
BRCA1				
Second grade 1	8	2	5	15
Second grade 2	2	2	17	21
Second grade 3	2	15	75	92
Total	12	19	97	128
BRCA2				
Second grade 1	3	4	0	7
Second grade 2	0	14	13	27
Second grade 3	1	7	7	15
Total	4	25	20	49

NOTE: P value < 0.0001 (χ^2 test) for *BRCA1*. P value = 0.003 (χ^2 test) for *BRCA2*.

Table 6. Association between histology of first and second cancers

	First ductal	First medullary	First lobular	First other	Total
BRCA1					
Second ductal	125	19	3	5	152
Second medullary	7	4	0	1	12
Second lobular	2	1	0	0	3
Second other	6	1	0	1	8
Total	140	25	3	7	175
BRCA2					
Second ductal	53	1	5	1	60
Second medullary	1	1	0	0	2
Second lobular	3	0	0	0	3
Second other	0	0	0	2	1
Total	57	2	5	2	66

NOTE: P value = 0.16 (Mantel-Haenszel χ^2 test) for *BRCA1*. P value = 0.80 (Mantel-Haenszel χ^2 test) for *BRCA2*.

concordant for histology, but this was not greater than expected (7).

Medullary tumors are more frequent in *BRCA1* carriers than in the general population, and represented 11% of the tumors in *BRCA1* carriers seen here, but did not tend to be concordant in the two breasts. In the general population, lobular cancers have been associated with a high rate of contralateral cancer, and we might have expected these to be found in excess here, but only 2.6% of the cases were classified as primarily lobular. It is possible that the difficulties associated with assigning histology are greater than for grade or for ER status and that a true underlying relationship was obscured by misclassification. Foulkes et al. have recently shown that the majority of *BRCA1*-associated breast cancers have a basal epithelium signature and this signature tends to be ER-negative (15). Using microarrays, Sorlie et al. observed a similar phenotype in *BRCA1*-associated breast cancers (16). It will be of interest in future studies to establish if the basal signature tends to be concordant in bilateral tumors.

The reason for the excess concordance in ER and grade in the bilateral cancers is unknown. It is unlikely that these findings are due to chance. It is possible that there has been some degree of misclassification in the assignment of ER status or tumor grade. It was necessary to conduct a multicenter study in order to generate an adequate sample size, and data were missing from 45% of the patients with bilateral cancer. Assays were not standardized across centers and there was no central pathology review. However, the effect of introducing misclassification bias into this study should be to reduce a true underlying effect, rather than to generate a spurious result.

Concordance might be expected if the second tumor was a metastasis of the first. It is not possible to formally rule out this possibility, but there is little evidence that the breast is a common site of metastases in *BRCA* mutation carriers. Patients who were known to have metastatic disease at, or prior to, the time of diagnosis of the contralateral cancer were excluded. Contralateral incidence is generally independent of the stage of the initial primary (17). Using somatic p53 mutation analysis, Janschek et al. found that 2 of 11 bilateral breast cancers shared the same p53 mutation (and hence were believed to be metastatic) and 9 of 11 were independent primaries (5).

If there are environmental or endogenous risk factors that determine the ER status of the tumors, then these factors might lead to similar characteristics of the two tumors. However, neither age nor any of the hormonal risk factors studied here were strongly predictive of ER status and none could explain the observed degree of concordance. The effect of initial ER status as a predictor of contralateral ER status was not diminished when age and hormonal factors were included in the model. This is in contrast to the National Surgical and Adjuvant Breast and Bowel Project data in nonhereditary cases showing a reduction in the incidence of ER-positive contralateral breast cancers in patients treated with tamoxifen for an initial ER-positive tumor (11). It is of course possible that other unknown risk factors are operating here; however, any single risk factor would have to have an extremely strong effect on ER status in order to generate results such as these.

Concordance of ER status might also be due to genetic factors, including allelic variation of the *BRCA* mutation or the presence of a modifier gene locus. Allelic variation might be responsible for some of the phenotypic difference in tumor characteristics, but thus far, it has not been shown that the probability of a breast cancer being ER-positive differs for different mutations in *BRCA1* or *BRCA2*. Hypothetically, there may be an allele of a polymorphic gene other than *BRCA1* or *BRCA2* that predicts the ER status of the cancer in an individual. To date, such a gene has not been identified in either the hereditary or nonhereditary populations. However, this genetic model is supported by the twin study of Peto and Mack (18). They found that the breast cancer risk of an affected identical twin was approximately double the risk of a contralateral breast cancer (in the general population). This

Table 7. Concordance for ER status by time interval between cancers

	Time between two cancers	ER status				OR	P
		(− −)	(− +)	(+ −)	(+ +)		
BRCA1	0-5 years	59	9	4	8	13.1	<0.0001
	≥5 years	40	4	9	3	3.3	0.14
BRCA2	0-5 years	2	2	3	26	8.7	0.04
	≥5 years	4	1	5	12	9.6	0.04

NOTE: (− −) First ER-negative, second ER-negative; (− +) first ER-negative, second ER-positive; (+ −) first ER-positive, second ER-negative; (+ +) first ER-positive; second ER-positive.

Table 8. Determinants of ER status of second breast cancer (*BRCA1* and *BRCA2* combined)

Variable	OR (95% CI)	P
Age of diagnosis	0.97 (0.93-1.01)	0.18
Tamoxifen use for first cancer (yes versus no)	0.71 (0.24-2.05)	0.52
Oophorectomy prior to second cancer (yes versus no)	0.65 (0.21-2.04)	0.46
ER status of first cancer (positive versus negative)	8.70 (3.52-21.5)	<0.0001
Gene (*BRCA2* versus *BRCA1*)	6.02 (2.29-15.9)	0.0003

Table 9. The OR of concordance of ER status by menopause

	Pre/post menopause	ER status				OR	P
		(− −)	(− +)	(+ −)	(+ +)		
BRCA1	first pre second pre	52	7	4	5	9.3	0.001
	first pre second post	21	4	5	5	5.3	0.04
	first post second post	15	2	2	1	3.8	0.33
BRCA2	first pre second pre	1	0	1	12	25.0*	0.01
	first pre second post	1	0	3	6	5.6	0.20
	first post second post	4	3	4	14	4.7	0.09

*Logit estimators, a correction of 0.5 applied if a cell contains a zero.

data fits the model that excess risk of bilateral cancers is due to genetic predisposition, but unfortunately, these authors do not provide data on pathologic markers for the breast cancers in the twins. *In utero* factors might be important as well. Although twins with *BRCA* mutations are rare, it is also possible to test for the existence of genetic factors by studying the ER status of breast cancers in other family members. These studies are now under way.

In the non-*BRCA* population, indices of genomic instability have been studied as possible predisposing factors for bilateral breast cancer. Bucholz and Wu found that women with bilateral breast cancer showed significantly higher levels of radiation-induced chromatid breaks than did healthy controls (19). Imyanitov and colleagues reported microsatellite instability in 15% of 46 bilateral breast cancers from 23 women (20).

It is also possible that some characteristic of the breast tissue itself might be a predictor of the ER status of the breast cancer when it arises, e.g., if mammographic breast density predicted the receptor status of the tumor, a high degree of concordance in ER status would be expected, given that breast density tends to be symmetrical. However, mammographic density has not been shown to relate to tumor receptor status. In a study of nonhereditary breast cancer patients Newman et al. (9) found that multicentricity was highly correlated with bilaterality (OR, 12.8; 95% CI, 4.5-37). This observation argues in support of the hypothesis that the host characteristic that predisposes to multifocality is present in both breasts.

Finally, our data are consistent with the hypothesis that both tumors are due to a common precursor lesion, i.e., that the ''field effect'' corresponds to a genetic or epigenetic phenomenon. Candidate lesions might include early loss of heterozygosity or the methylation status of the *BRCA* gene or other genes in the carcinogenic pathway. This model is unorthodox in that to be bilateral the precursor lesion would have to be inherited, or arise early in embryogenesis, or be the result of spread from a common site. Recent *in vitro* and *in vivo* evidence suggests the existence of adult mammary epithelial stem cells in the normal breast (reviewed in Smalley and Ashworth, ref. 21), and that these cells might be responsible for the massive expansion in the breast during pregnancy as well as the cell of origin of most breast tumors. Excess concordance for ER status could arise if stem cells with a second (acquired) mutation populate both breasts. Taken collectively with the findings of our study, there is support for the concept of a common precursor cell and prompts consideration of the possible function of *BRCA1* in breast stem cells and normal and abnormal development. Imyanitov and colleagues compared molecular profiles in 28 bilateral breast cancers (22). For 27 tumors, molecular analyses excluded metastatic disease. Bilateral tumors were more likely to be similar for the allelic imbalance marker profiles if they were synchronous or if both presented premenopausally.

None of the models described here adequately explains why synchronous tumors are more likely to be concordant than asynchronous tumors. Our data compels us to conclude that a significant proportion of bilateral cancers are due to a common effect, although for some proportion of women, the cancers (in particular, asynchronous tumors) undoubtedly are independent events. These findings have additional implications for early processes in cancer. If cancers or their precursor lesions were to switch from ER-positive to ER-negative early in carcinogenesis, then little correlation in receptor status for large tumors would be observed. Our findings suggest that ER status and grade are inherent features of the tumors and are to some extent predetermined (by as yet unknown factors). If cancers or their precursor lesions were to switch from ER-positive to ER-negative early in carcinogenesis, then we would not expect to see concordance of ER status to the extent observed here. Our findings favor a contrasting model in which ER status and grade are invariant throughout the evolution of the cancer.

Acknowledgments

We thank Mandy Whitlock and Veronica Lagos for technical support; Ellen Warner, Kenneth Offit, Peter Ainsworth, Judy Garber, Hakan Olsson, Howard Saal, Fergus Couch, Mary Daly, Gareth Evans, Michael Osborne, Wendy McKinnon, Marie Wood, Andrea Eisen, Charis Eng, Kevin Sweet, Rebecca Sutphen, and Ab Chudley for their contribution of patients to this study.

References

1. Ford D, Easton DF, Stratton M, et al. Genetic heterogeneity and penetrance analysis of the *BRCA1* and *BRCA2* genes in breast cancer families. The Breast Cancer Linkage Consortium. Am J Hum Genet 1998;62:676–89.
2. Struewing JP, Hartge P, Wacholder S, et al. The risk of cancer associated with specific mutations of *BRCA1* and *BRCA2* among Ashkenazi Jews. N Engl J Med 1997;336:1401–8.
3. Ford D, Easton DF, Bishop DT, et al. Risks of cancer in *BRCA1*-mutation carriers. Lancet 1994;343:692–5.
4. Metcalfe K, Lynch HT, Ghadirian P, et al. Contralateral breast cancer in BRCA1 and BRCA2 mutation carriers. J Clin Oncol 2004;22:2328–35.
5. Janschek E, Kandioler-Eckersberger D, Ludwig C, et al. Contralateral breast cancer: molecular differentiation between metastasis and second primary cancer. Breast Cancer Res Treat 2001;67:1–8.
6. Kiang DT, Kennedy BJ, Snover DC. Biological and histological characteristics of simultaneous bilateral breast cancer. Lancet 1980;2:1105–7.
7. Gogas J, Markopoulos C, Skandalakis P, Gogas H. Bilateral breast cancer. Am Surg 1993;59:733–5.
8. Matsuo K, Fukutomi T, Tsuda H, et al. Differences in estrogen receptor status, HER2, and p53 comparing metachronous bilateral breast carcinoma. J Surg Oncol 2001;77:31–4.
9. Newman LA, Sahin AA, Cunningham JE, et al. A case-control study of unilateral and bilateral breast carcinoma patients. Cancer 2001;91:1845–53.
10. Coradini D, Oriana S, Mariani L, et al. Is steroid receptor profile in contralateral breast cancer a marker of independence of the corresponding primary tumour? Eur J Cancer 1998;34:825–30.
11. Swain SM, Wilson JW, Mamounas EP, et al. Estrogen receptor status of primary breast cancer is predictive of estrogen receptor status of contralateral breast cancer. J Natl Cancer Inst 2004;96:516–23.
12. Kollias J, Pinder SE, Denley HE, et al. Phenotypic similarities in bilateral breast cancer. Breast Cancer Res Treat 2004;85:255–61.
13. Harvey EB, Brinton LA. Second cancer following cancer of the breast in Connecticut, 1935–82. Natl Cancer Inst Monogr 1985;68:99–112.
14. Narod SA, Brunet JS, Ghadirian P, et al. Tamoxifen and risk of contralateral breast cancer in BRCA1 and BRCA2 mutation carriers: a case-control study. Hereditary Breast Cancer Clinical Study Group. Lancet 2000;356:1876–81.
15. Foulkes WD, Stefansson IM, Chappuis PO, et al. Germline BRCA1 mutations and a basal epithelial phenotype in breast cancer. J Natl Cancer Inst 2003; 95:1482–5.
16. Sorlie T, Tibshirani R, Parker J, et al. Repeated observation of breast tumor subtypes in independent gene expression data sets. Proc Natl Acad Sci U S A 2003;100:8418–23.
17. Bernstein JL, Thompson WD, Risch N, Holford TR. Risk factors predicting the incidence of second primary breast cancer among women diagnosed with a first primary breast cancer. Am J Epidemiol 1992;136:925–36.
18. Peto J, Mack TM. High constant incidence in twins and other relatives of women with breast cancer. Nat Genet 2000;26:411–4.
19. Buchholz T, Wu X. Radiation-induced chromatid breaks as a predictor of breast cancer risk. Int J Radiat Oncol Biol Phys 2001;49:533–7.
20. Imyanitov EN, Togo AV, Suspitsin EN, et al. Evidence for microsatellite instability in bilateral breast carcinomas. Cancer Lett 2000;154:9–17.
21. Smalley M, Ashworth A. Stem cells and breast cancer: a field in transit. Nat Rev Cancer 2003;3:832–44.
22. Imyanitov EN, Suspitsin EN, Grigoriev MY, et al. Concordance of allelic imbalance profiles in synchronous and metachronous bilateral breast carcinomas. Int J Cancer 2002;100:557–64.

A Comparison of Bilateral Breast Cancers in *BRCA* Carriers

Jeffrey N. Weitzel, Mark Robson, Barbara Pasini, et al.

Cancer Epidemiol Biomarkers Prev 2005;14:1534-1538.