VOLUME 22 · NUMBER 6 · MARCH 15 2004

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Bilateral Prophylactic Mastectomy Reduces Breast Cancer Risk in *BRCA1* and *BRCA2* Mutation Carriers: The PROSE Study Group

Timothy R. Rebbeck, Tara Friebel, Henry T. Lynch, Susan L. Neuhausen, Laura van 't Veer, Judy E. Garber, Gareth R. Evans, Steven A. Narod, Claudine Isaacs, Ellen Matloff, Mary B. Daly, Olufunmilayo I. Olopade, and Barbara L. Weber

From the PROSE Study Group; the Center for Clinical Epidemiology and Biostatistics, Abramson Family Cancer Research Institute, The University of Pennsylvania; and Fox Chase Cancer Center, Philadelphia, PA; Creighton University, Omaha, NE; Division of Genetic Epidemiology, Department of Medicine, University of California Irvine, Irvine, CA; Women's College Hospital, Toronto, Ontario, Canada; the Netherlands Cancer Institute, Amsterdam, the Netherlands; Dana-Farber Cancer Institute, Boston, MA; St. Mary's Hospital, Manchester, United Kingdom; Lombardi Cancer Center, Georgetown University, Washington, DC; Yale University, New Haven, CT; and University of Chicago, Chicago, IL. A list of additional PROSE Study Group members and affiliations appears in the Appendix (online only).

Submitted April 28, 2003; accepted November 3, 2003.

Supported by grants from the National Institutes of Health (grant Nos. R01-CA83855 to T.R.R. and B.L.W.; CA57601 to B.L.W.; and CA74415 to S.L.N.), the Abramson Cancer Center (T.R.R.), the Abramson Family Cancer Research Institute (B.L.W.), the Breast Cancer Research Foundation (B.L.W.), the Dana-Farber Women's Cancers Program (J.E.G.), the Department of Defense (grant Nos. DAMD-17-96-I-6088 to A.K.G., DAMD-17-94-J-4340 and DAMD-17-99-1-9123 to O.I.O., and DAMD-17-97-I-7112 to H.T.L.), the Utah Cancer Registry (funded by a National Institutes of Health grant No. NO1-CN-6700, the Falk Medical Research Trust [O.I.O.], and the Utah State Department of Health), and the Nebraska State Cancer and Smoking-Related Diseases Research Program (grant No. LB595 to H.T.L.). O.I.O. is a Doris Duke Distinguished Clinical Scientist.

Authors' disclosures of potential conflicts of interest are found at the end of this article.

Address reprint requests to Barbara L. Weber, MD, Abramson Family Cancer Research Institute, University of Pennsylvania, 514 BRB2, 421 Curie Blvd, Philadelphia, PA 19104-6021; e-mail: weberb@mail.med.upenn.edu.

0732-183X/04/2206-1055/$20.00

DOI: 10.1200/JCO.2004.04.188

ABSTRACT

Purpose
Data on the efficacy of bilateral prophylactic mastectomy for breast cancer risk reduction in women with *BRCA1* and *BRCA2* (*BRCA1/2*) mutations are limited, despite the clinical use of this risk-management strategy. Thus, we estimated the degree of breast cancer risk reduction after surgery in women who carry these mutations.

Patients and Methods
Four hundred eighty-three women with disease-associated germline *BRCA1/2* mutations were studied for the occurrence of breast cancer. Cases were mutation carriers who underwent bilateral prophylactic mastectomy and who were followed prospectively from the time of their center ascertainment and their surgery, with analyses performed for both follow-up periods. Controls were *BRCA1/2* mutation carriers with no history of bilateral prophylactic mastectomy matched to cases on gene, center, and year of birth. Both cases and controls were excluded for previous or concurrent diagnosis of breast cancer. Analyses were adjusted for duration of endogenous ovarian hormone exposure, including age at bilateral prophylactic oophorectomy if applicable.

Results
Breast cancer was diagnosed in two (1.9%) of 105 women who had bilateral prophylactic mastectomy and in 184 (48.7%) of 378 matched controls who did not have the procedure, with a mean follow-up of 6.4 years. Bilateral prophylactic mastectomy reduced the risk of breast cancer by approximately 95% in women with prior or concurrent bilateral prophylactic oophorectomy and by approximately 90% in women with intact ovaries.

Conclusion
Bilateral prophylactic mastectomy reduces the risk of breast cancer in women with *BRCA1/2* mutations by approximately 90%.

J Clin Oncol 22:1055-1062. © 2004 by American Society of Clinical Oncology

INTRODUCTION

Women with germline *BRCA1* or *BRCA2* (*BRCA1/2*) mutations have a markedly increased risk of breast and ovarian cancer compared with the general population [1-3]. These women sometimes elect bilateral prophylactic mastectomy to reduce their risk of breast cancer. However, data on breast cancer risk reduction after bilateral prophylactic mastectomy in this high-risk group are limited. Hartmann et al [4] evaluated the efficacy of bilateral prophylactic mastectomy in a retrospective cohort analysis of 639 moderate- and high-risk women who had bilateral prophylactic mastectomy at the Mayo Clinic between 1960 and 1993. Data from this study suggest that bilateral prophylactic mastectomy is associated with a 90% reduction in breast cancer incidence and mortality in women at high risk of breast cancer. However, *BRCA1/2* mutation status was unavailable for the initial analysis, and only 18 women in this series were later reported to be *BRCA1/2* mutation carriers [5]. Postbilateral prophylactic mastectomy breast

Table 1. Description of Characteristics and Exclusion Criteria for Analyses 1 Through 4

Analysis No.	Patients Who Had Bilateral Prophylactic Mastectomy (No.)	Controls (No.)	Excluded for Bilateral Prophylactic Mastectomy or Breast Cancer Diagnosis Before Ascertainment	Excluded for Bilateral Prophylactic Oophorectomy Before or Concurrent With Bilateral Prophylactic Mastectomy
1	102	378	No	No
2	59	305	No	Yes
3	57	107	Yes	No
4	28	69	Yes	Yes
Total	105	378		

cancer risk reduction in this small group of mutation carriers was estimated at 89% to 100%, but the 95% CIs were large.

In the only other study of *BRCA1/2* mutation carriers to date, Meijers-Heijboer et al [6] reported no postbilateral prophylactic mastectomy breast cancers in 76 *BRCA1/2* mutation carriers after 2.9 years of follow-up, compared with eight breast cancers in 63 mutation carriers who did not undergo bilateral prophylactic mastectomy ($P = .003$). These data suggest that bilateral prophylactic mastectomy confers substantial breast cancer risk reduction in *BRCA1/2* mutation carriers, but accurate estimates of the magnitude of this risk reduction could not be determined from this study. We measured the incidence of breast cancer in 483 *BRCA1/2* mutation carriers (105 surgical subjects and 378 matched controls) using a case-control sample drawn from a historical cohort using an incidence density sampling design.

PATIENTS AND METHODS

Study Participants

Women with germline, disease-associated *BRCA1/2* mutations were identified from 11 North American and European institutions (Creighton University, The Dana-Farber Cancer Institute, The Fox Chase Cancer Center, Georgetown University, University of Chicago, University of Pennsylvania, University of Utah, the Netherlands Cancer Institute, St. Mary's Hospital, Women's College Hospital, and Yale University). The *BRCA1/2* mutation status of all subjects was confirmed by direct mutation testing with full informed consent under protocols approved by the human subjects review boards at each institution. Women with *BRCA1/2* variants of unknown functional significance were excluded. Two groups of women were studied. First, we studied women who underwent bilateral prophylactic mastectomy. Second, we studied controls without either bilateral prophylactic mastectomy or breast cancer at the time of the matched subject's surgery. One or more controls were selected per surgical subject if they could be matched on type of mutation, treatment center, and year of birth within 5 years. Study participants were excluded if they had prior or concurrent breast cancer at time of surgery. Women who underwent prophylactic mastectomy had one of the following four surgical procedures (if known) as noted in Table 1: total (simple) mastectomy (ie, removal of both breasts and overlying skin without axillary dissections); subcutaneous mastectomy (ie, removal of both breasts with preservation of overlying skin and nipple-areolar complexes); modified radical mastectomy (ie, removal of both breasts with overlying skin and axillary contents); and radical mastectomy (ie, removal of both breasts with overlying skin, pectoralis muscles, and axillary contents). All procedures were confirmed by medical record and/or pathology reports as prophylactic, not therapeutic.

As summarized in Table 1, four analyses were performed to fully explore the breast cancer risk reduction associated with bilateral prophylactic mastectomy and to consider the effects of oophorectomy on this risk reduction. Cases and controls were observed prospectively from the time of their center ascertainment and surgery (cases only), with analyses performed for both follow-up periods. In an attempt to eliminate selection bias potentially introduced by women with a documented previous breast cancer diagnosis, a second set of analyses was preformed using only cases and controls that had not had bilateral prophylactic mastectomy at the time of center ascertainment. Therefore, for analyses 3 and 4, controls were also matched on year of ascertainment. In addition, analyses 1 and 3 were adjusted for duration of endogenous ovarian hormone exposure, including age at bilateral prophylactic oophorectomy. The total sample from which individuals were drawn included 483 women, including 105 who underwent bilateral prophylactic mastectomy and 378 who did not. Analysis 1 was the largest sample, including 480 individuals (99.4%) of the total sample size. Three eligible bilateral prophylactic mastectomy subjects were not included in Analysis 1 because matching of 102 bilateral prophylactic mastectomy subjects exhausted the availability of all 378 controls. Because not all bilateral prophylactic mastectomy subjects were eligible for analyses 2, 3, and 4, controls became available, and these three cases were included in these analyses. For each analysis, controls were rematched to all eligible bilateral prophylactic mastectomy subjects, respecting each specific sample set criteria (Table 1), to achieve the largest possible sample sizes.

Analysis 1 (follow-up from center ascertainment, all cases and controls). Four hundred eighty study participants were included in this analysis regardless of their bilateral prophylactic mastectomy, bilateral prophylactic oophorectomy, or breast cancer status at the time of center ascertainment. Cases were eligible if they had a disease-associated *BRCA1/2* mutation, had undergone bilateral prophylactic mastectomy, and had not been diagnosed with breast or ovarian cancer before bilateral prophylactic mastectomy. Controls were eligible if they were alive and cancer-free with both breasts intact at the time of the matched subject's bilateral prophylactic mastectomy. Survival analyses were adjusted to account for duration of endogenous ovarian hormone exposure as measured

by the time from age at menarche to age at bilateral prophylactic oophorectomy or menopause, whichever was sooner. Thus, this is a mixed prospective and retrospective analysis of bilateral prophylactic mastectomy effect adjusted for duration of endogenous ovarian hormone exposure that included 102 bilateral prophylactic mastectomy subjects and 378 controls.

Analysis 2 (follow-up from center ascertainment, no prior or concurrent bilateral prophylactic oophorectomy). This analysis was performed on the subset of women from the total sample who had undergone bilateral prophylactic mastectomy but had not undergone bilateral prophylactic oophorectomy before this procedure. Controls were eligible if they had not undergone bilateral prophylactic oophorectomy and were alive and cancer-free with both breasts intact at the time of the matched subject's bilateral prophylactic mastectomy. Thus, this is an analysis of bilateral prophylactic mastectomy effect in *BRCA1/2* mutation carriers with no prior or concurrent bilateral prophylactic oophorectomy that included 59 bilateral prophylactic mastectomy subjects and 305 controls.

Analysis 3 (follow-up from bilateral prophylactic mastectomy after center ascertainment). This analysis was performed on the subset of women who had not had bilateral prophylactic mastectomy at the time of their center ascertainment. Controls were excluded if they had a diagnosis of breast or ovarian cancer at or before the time of the matched surgical subject's bilateral prophylactic mastectomy. As in analysis 1, surgical subjects and matched controls were included regardless of their history of bilateral prophylactic oophorectomy, and survival analyses were adjusted to account for the duration of exposure to endogenous ovarian hormones. Thus, this is a prospective analysis of bilateral prophylactic mastectomy effect adjusted for duration of endogenous ovarian hormone exposure that included 57 bilateral prophylactic mastectomy subjects and 107 controls.

Analysis 4 (follow-up from bilateral prophylactic mastectomy after center ascertainment, no prior or concurrent bilateral prophylactic oophorectomy). This analysis was performed on the subset of women who had not had bilateral prophylactic mastectomy at the time of their center ascertainment and had not undergone bilateral prophylactic oophorectomy at or before bilateral prophylactic mastectomy. Controls were ineligible if they had a diagnosis of breast or ovarian cancer or had undergone bilateral prophylactic oophorectomy at or before the time of the matched surgical subject's bilateral prophylactic mastectomy. Thus, this is a prospective analysis of bilateral prophylactic mastectomy effect in the absence of bilateral prophylactic oophorectomy that included 28 bilateral prophylactic mastectomy subjects and 69 controls.

Data Collection and Statistical Analysis

Entry and follow-up at each center were undertaken without regard to surgical status. Vital status and cancer diagnoses were obtained using telephone interviews and/or self-administered questionnaires and verified with medical records, pathology reports, and/or cancer registries. Reproductive and smoking history, exogenous hormone use, and alcohol consumption were obtained by questionnaire. For women who had died since center ascertainment, medical records were used to verify information provided by family members.

Cox proportional hazards models were used to estimate differences in cancer incidence by bilateral prophylactic mastectomy status using STATA (release 7; STATA Corp, College Station, TX). A robust variance-covariance estimation method [7] was used to correct for nonindependence of observations among subjects from the same family. Surgical subjects and controls were observed from the date of the surgical subject's bilateral prophylactic mastectomy until a diagnosis of breast cancer or a censoring event. Subjects were censored at the date they developed ovarian cancer, underwent bilateral prophylactic oophorectomy (analyses 2 and 4 only), or died, or at the date of last contact. Diagnosis of invasive breast cancer or ductal carcinoma-in-situ was considered the primary event of interest.

Table 2. Descriptive Sample Characteristics

Characteristic	Bilateral Prophylactic Mastectomy	Controls
Sample size, No. of patients	105	378
Birth year		
Mean	1955.7	1952.0
Range	1916-1970	1911-1970
Age at bilateral prophylactic mastectomy, years		
Mean	38.1	—
Range	20.6-63.4	—
Year of prophylactic mastectomy		
Mean	1992.7	—
Range	1967-2001	—
Breast cancers, No.	2	184
Age at diagnosis, years		
Mean	35.3	41.3
Range	28.7-41.9	24.0-77.5
Years of follow-up to diagnosis		
Mean	5.7	6.0
Range	2.3-9.2	0.89-31.9
Years of follow-up to censoring		
Mean	5.3	7.5
Range	0-31.1	0.02-33.8
No. of women-years	557.36	2551.17

RESULTS

Characteristics of the entire sample are listed in Table 2. Characteristics of the bilateral prophylactic mastectomy subjects and matched controls by analysis are listed in Tables 3 and 4. Mean age at time of surgery for the whole sample was 38.1 years. Follow-up of controls began at a mean age of 36.3 years. Postsurgery follow-up duration was 5.5 years in cases and 6.7 years in controls. Of the 105 mutation carriers with bilateral prophylactic mastectomy (cases) in the total cohort, two (1.9%) were diagnosed with breast cancer after bilateral prophylactic mastectomy (both subcutaneous) compared with 184 (48.7%) of 378 controls. Two additional controls developed breast cancer but were censored because of a prior diagnosis of ovarian cancer. Pathology records of the two women with postbilateral prophylactic mastectomy breast cancer indicated no detectable evidence of breast cancer at the time of prophylactic surgery. These breast cancers occurred 2.3 and 9.2 years after bilateral prophylactic mastectomy. Figure 1 presents a Kaplan-Meier analysis of breast cancer events by postsurgery follow-up time in cases compared with controls.

Table 3. Bilateral Prophylactic Mastectomy: Participant Characteristics for Analyses 1 and 2

Characteristic	Analysis 1 (ovarian hormone exposure adjusted)					Analysis 2 (no prior or concurrent oophorectomy)				
	Bilateral Prophylactic Mastectomy (n = 102)		Controls (n = 378)			Bilateral Prophylactic Mastectomy (n = 59)		Controls (n = 305)		
	No.	%	No.	%	P*	No.	%	No.	%	P*
Year of birth										
Mean	1955.5		1952.0		< .001	1956.6		1952.5		< .001
Range	1916-1970		1911-1970			1935-1970		1931-1970		
Mastectomy type										
Subcutaneous	29	28.7	—	—	—	22	37.2	—	—	—
Total	47	46.5	—	—	—	24	40.7	—	—	—
Radical or modified radical	3	3.0	—	—	—	2	3.4	—	—	—
Approach not specified	23	22.5	—	—	—	11	18.6	—	—	—
Parous†	87	86.1	297	79.6	.15	50	86.2	244	80	.46
Parity										
Mean	2.5		2.4		.44	2.5		2.4		.77
Range	1-7		1-7			1-5		1-7		
Age at menarche, years										
Mean	13.3		12.6		< .001	13.3		12.6		< .001
Range	10-18		8-18			10-18		8-18		
Age at first live birth, years										
Mean	25.3		24.8		.39	24.5		24.8		.71
Range	15-42		15-9			16-36		15-39		
Oral contraceptive use†‡	79	83.2	282	82.2	.88	48	85.7	237	84.9	.99
Hormone replacement use†‡	61	65.6	112	35.9	< .001	28	52.8	96	38.2	.06
% *BRCA1*	—	78.4	—	79.9	.78	—	74.6	—	82.3	.20

*Comparison of bilateral prophylactic mastectomy subjects and controls using Fisher's exact test for discrete variables or Wilcoxon rank sum test for continuous variables.
†Percentages calculated using nonmissing data.
‡Ever use of oral contraceptive or hormone replacement therapy.

The first postsurgery breast cancer case had an R2520X mutation in *BRCA2* and underwent bilateral prophylactic mastectomy at age 26 years. Twenty-seven months later, at age 28 years, a palpable axillary mass was found to be metastatic adenocarcinoma in an axillary lymph node consistent with a breast primary. No primary or metastatic tumor was identified elsewhere by bone scan, abdominal computed tomography scan, or chest x-ray. The second postsurgery breast cancer case had a 188del11 mutation in *BRCA1* and underwent bilateral prophylactic mastectomy at age 32 years. Nine years later, she was diagnosed with ductal carcinoma-in-situ and an adjacent stage II infiltrating ductal carcinoma in substantial residual right breast tissue. This subject was later diagnosed with poorly differentiated grade 3 ovarian cancer of mixed serous and mucinous histology at age 47 years.

Compared with controls, the occurrence of postbilateral prophylactic mastectomy breast cancer in cases corresponds to a hazard ratio of 0.05 to 0.09 (Table 5, analyses 1 and 2), confirming a substantial and statistically significant reduction in breast cancer risk after bilateral prophylactic mastectomy in *BRCA1/2* mutation carriers. In the most rigorous analysis, no women with bilateral prophylactic mastectomy in the purely prospective groups (analyses 3 and 4) were diagnosed with breast cancer after 3.0 and 2.9 mean years of follow-up, respectively, compared with 24 of 107 controls in analysis 3 ($P < .001$) and 19 of 69 controls in analysis 4 ($P < .001$; Table 4). The absence of postbilateral prophylactic mastectomy breast cancers precludes formal estimation of the magnitude of risk reduction associated with bilateral prophylactic mastectomy in the purely prospective analyses.

DISCUSSION

These data indicate that bilateral prophylactic mastectomy reduces the risk of breast cancer by approximately 90% in *BRCA1/2* mutation carriers. Assuming a breast cancer risk to age 70 years of 73% in the clinic-based populations studied here [8], this 90% risk reduction translates into a breast cancer risk in *BRCA1/2* mutation carriers of 7% to age 70 years. Although formal analyses have yet to be performed because of insufficient follow-up time and number of deaths in our sample, it can be inferred that this risk reduction will be associated with a marked reduction in breast cancer mortality.

Table 4. Bilateral Prophylactic Mastectomy: Participant Characteristics for Analyses 3 and 4

Characteristic	Analysis 3 (ovarian hormone exposure adjusted)					Analysis 4 (no prior or concurrent oophorectomy)				
	Bilateral Prophylactic Mastectomy (n = 57)		Controls (n = 107)			Bilateral Prophylactic Mastectomy (n = 28)		Controls (n = 69)		
	No.	%	No.	%	*P**	No.	%	No.	%	*P**
Year of birth										
Mean	1958.5		1958.5		.99	1959.5		1958.1		.33
Range	1933-1970		1937-1971			1993-1968		1938-1969		
Mastectomy type										
Subcutaneous	13	22.8	—	—	—	11	39.3	—	—	—
Total	28	49.1	—	—	—	12	42.9	—	—	—
Radical or modified radical	0	0	—	—	—	0	0	—	—	—
Approach not specified	16	28.1	—	—	—	5	17.9	—	—	—
Parous†	48	85.7	73	71.6	.05	24	88.9	52	76.5	.26
Parity										
Mean	2.4		2.1		.07	2.4		2.1		.15
Range	1-7		1-4			1-5		1-4		
Age at menarche, years										
Mean	13.2		12.7		.01	13.4		12.5		.01
Range	10-18		9-16			10-18		9-16		
Age at first live birth, years										
Mean	27.2		25.7		.12	25.9		25.6		.83
Range	16-42		15-37			16-36		18-35		
Oral contraceptive use†‡	44	88	80	86.0	.80	22	88.0	55	88.7	.99
Hormone replacement use†‡	33	64.7	119	46.2	.05	14	58.3	22	43.1	.32
% *BRCA1*	—	84.2	—	86.9	.64	—	71.4	—	84.1	.17

*Comparison of bilateral prophylactic mastectomy subjects and controls using Fisher's exact test (for discrete variables) or Wilcoxon rank sum test (for continuous variables).
†Percentages calculated using nonmissing data.
‡Ever use oral contraceptive or hormone replacement therapy.

Our estimates of risk reduction are consistent with previous reports of the efficacy of bilateral prophylactic mastectomy in women with unknown *BRCA1/2* mutation status. In the retrospective cohort analysis by Hartmann et al [4], bilateral prophylactic mastectomy was associated with a 90% reduction in expected breast cancer incidence and mortality in both the moderate- and high-risk groups. As in the current study, all postbilateral prophylactic mastectomy breast cancers occurred after subcutaneous mastectomy. In a study of 139 *BRCA1/2* mutation carriers, Meijers-Heijboer et al [6] compared the observed versus expected proportion of breast cancer in 76 mutation carriers who underwent bilateral prophylactic mastectomy and 63 mutation carriers who did not have the procedure. No cases of breast cancer were diagnosed after bilateral prophylactic mastectomy compared with eight diagnosed breast cancers after 3 years of follow-up in women who did not have the surgery. Together with the current study, these analyses conclusively demonstrate significant and substantial breast cancer risk reduction after bilateral prophylactic mastectomy in *BRCA1/2* mutation carriers.

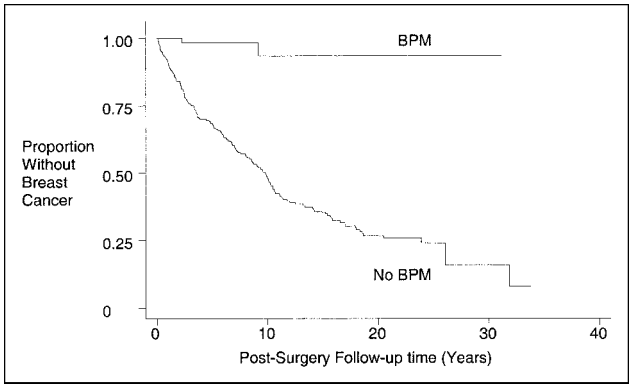

Fig 1. Time to breast cancer diagnosis in female *BRCA1* mutation carriers with and without bilateral prophylactic mastectomy (BPM).

Although a prospective, randomized clinical trial would be the methodologically ideal approach to evaluate the efficacy of bilateral prophylactic mastectomy, such a trial is not feasible because few women would agree to be randomly assigned to bilateral prophylactic mastectomy versus observation. Similarly, a purely prospective study design would limit chances that selection or survival biases would influence the estimate of risk reduction associated with bilateral prophylactic mastectomy. However, the number of mutation carriers and length of time required for

Table 5. Effect of Bilateral Prophylactic Mastectomy on Breast Cancer Risk Reduction

Characteristic	Prophylactic Surgery Before Center Ascertainment Allowed		Prophylactic Surgery Before Center Ascertainment Excluded	
	Analysis 1 (prior or concurrent oophorectomy allowed)	Analysis 2 (no prior or concurrent oophorectomy)	Analysis 3 (prior or concurrent oophorectomy allowed)	Analysis 4 (no prior or concurrent oophorectomy)
Total subjects, No.	480	364	164	97
Bilateral prophylactic mastectomy	102	59	57	28
Controls	378	305	107	69
Birth year				
Bilateral prophylactic mastectomy				
Mean	1955.5	1956.6	1958.5	1959.5
Range	1916-1970	1935-1970	1933-1970	1943-1968
Controls				
Mean	1951.9	1952.6	1958.5	1958.1
Range	1911-1970	1931-1970	1937-1970	1938-1969
Age at surgery, years				
Bilateral prophylactic mastectomy				
Mean	38.1	35.4	38.3	36.4
Range	20.6-63.4	20.6-51.1	21.3-63.4	21.3-51.0
Controls				
Mean	36.3	34.2	37.8	35.7
Range	17.4-65.1	17.4-55.9	23.7-58.1	23.7-56.0
Breast cancers				
Bilateral prophylactic mastectomy, No.	2	2	0	0
Controls, No.	184	149	24	19
P	< .0001	< .0001	< .0001	< .0001
Age at diagnosis, years				
Bilateral prophylactic mastectomy				
Mean	35.3	35.3	—	—
Range	28.7-41.9	28.7-41.9	—	—
Controls				
Mean	41.3	40.3	39.4	39.2
Range	24.0-77.5	24.0-63.1	29.7-56.6	29.7-56.6
Years of follow-up to diagnosis				
Bilateral prophylactic mastectomy				
Mean	5.7	5.7	—	—
Range	2.3-9.2	2.3-9.2	—	—
Controls				
Mean	6.0	6.8	1.3	2.3
Range	0.09-31.9	0.03-31.9	0.1-4.8	0.5-10.2
Years of follow-up to censoring				
Bilateral prophylactic mastectomy				
Mean	5.4	4.8	3.0	2.9
Range	0-31.1	0.02-30.5	0.0-13.0	0.1-13.0
Controls				
Mean	7.5	7.1	2.3	2.9
Range	0.02-33.8	0.02-24.3	0.02-11.5	0.1-11.7
Adjusted hazard ratio	0.05	0.09	0	0
95% CI	0.01-0.22	0.02-0.38	—	—

such a study would preclude us from providing women with an assessment of the efficacy of bilateral prophylactic mastectomy for the foreseeable future. In this study, we analyzed both our total cohort and the purely prospective subset of women who had bilateral prophylactic mastectomy after center ascertainment. Potential sources of bias in our study design include confounding by indication and competing events [9]. Confounding by indication could affect the analyses if the reasons for undergoing bilateral prophylactic mastectomy are related to risk of breast cancer. Under this scenario, controls at greater risk of developing breast cancer would have to be less likely to undergo surgery than women with less risk. Although unlikely, this effect would lead to an underestimation in risk reduction. Because we estimated risk reduction at close to 95%, the possible underestimation of risk reduction is minimal at

best. Competing events, particularly ovarian cancer, also could affect the cancer characteristics of the sample. However, our analyses specifically excluded women who developed cancer before the time of bilateral prophylactic mastectomy in both cases and controls. Thus, our analyses were well matched with respect to prior events and censored both bilateral prophylactic mastectomy and nonbilateral prophylactic mastectomy groups if an ovarian cancer was diagnosed. Although the age-adjusted cumulative breast cancer risk in the controls described in this study is somewhat but not significantly higher than that of other studies of preventive surgery (eg, 184 breast cancer cases in 2,551 person-years of follow-up *v* eight breast cancers in 190 person-years of follow-up in the Dutch study [6]), the overall breast cancer risk in the current study is approximately 50% by age 50 years, with a mean age of diagnosis of 41.3 years. These values are not substantially different than those of the penetrance reported in multiple studies of women with *BRCA1* or *BRCA2* mutations [10,11]. Additionally, the sample used for the current study is representative of the population of women who attend high-risk clinics for genetic testing and discussion of risk-management options. Thus, we are able to estimate breast cancer risk reduction using a matched study design that corrects for many of the limitations of a mixed prospective-retrospective cohort design while circumventing the time and study size considerations of a purely prospective study.

In this study, only two women were diagnosed with breast cancer after bilateral prophylactic mastectomy; thus, we cannot make strong inferences about optimal type and timing of surgery or about risk factors that may influence postbilateral prophylactic mastectomy breast cancers. However, both failures occurred in women with subcutaneous mastectomies. Unfortunately, one of the failures (and the subsequent death of the patient) likely would have occurred regardless of the type of procedure because it most probably represented microscopic primary breast cancer metastatic to axillary lymph nodes at the time of surgery. However, the other failure may have been preventable because this woman developed a noninvasive breast cancer that progressed to invasive disease in residual breast epithelium. In our cohort, about one third of women in whom surgical procedure could be unequivocally determined underwent subcutaneous mastectomy. Subcutaneous bilateral prophylactic mastectomy leaves substantial residual breast tissue intact, including the nipple-areolar complex and, therefore, is not optimal for a prophylactic procedure. Total mastectomy requires more extensive reconstruction and may result in an inferior cosmetic result, but it removes substantially more breast tissue. However, the recently developed skin-sparing mastectomy with immediate reconstruction combines adequate tissue removal with excellent cosmetic outcome [12]. Thus, this procedure is an excellent choice for bilateral prophylactic mastectomy where a qualified general or plastic surgical team is available. Regardless of the selected procedure, care should be taken to remove as much breast tissue as possible to maximize risk reduction.

There are surgical and anesthetic risks that should be considered when offering prophylactic surgery to a healthy individual [13]. In a recent series of 112 high-risk women (79 with a *BRCA1/2* mutation) who underwent prophylactic mastectomy (103 with immediate reconstruction), 21% had complications, including hematoma, infection, contracture, or implant rupture [14]. Use of autologous tissue, such as with transverse rectus abdominis musculocutaneous (TRAM) or latissimus dorsi reconstruction, may eliminate the need for silicone implants, but complication rates may be even higher. In one series of 147 breast cancer patients with TRAM reconstruction after mastectomy, follow-up operations were necessary in 71% of patients, including intervention for complications such as abdominal hernia, full or partial TRAM ischemic loss, and fat necrosis [15].

Our long-term goal is to provide effective nonsurgical breast cancer prevention to all high-risk women. Numerous epidemiologic studies suggest that breast cancer risk in *BRCA1/2* mutation carriers is influenced by estrogen exposure in a manner analogous to that of the general population [16]. This effect is also seen in the 50% breast cancer risk reduction we reported in association with bilateral prophylactic oophorectomy [7,17]. These findings suggest that breast cancer risk in *BRCA1/2* mutation carriers is likely to be reduced by chemopreventive agents such as tamoxifen. Unfortunately, the Breast Cancer Prevention Trial data do not provide adequate information on chemoprevention in women with *BRCA1* mutations. Because only eight *BRCA1* mutation carriers were diagnosed with breast cancer in the Breast Cancer Prevention Trial [18] (five on tamoxifen and three on placebo) and the results were not statistically significant from that small sample (odds ratio, 1.67; 95% CI, 0.41 to 8.00), conclusions cannot be drawn regarding tamoxifen efficacy in this setting. Although limited inferences can be drawn from retrospective studies, many studies suggest that reducing estrogen effect on breast tissue, including by tamoxifen administration [19], reduces breast cancer risk in *BRCA1* mutation carriers.

In summary, bilateral prophylactic mastectomy significantly reduces the risk of breast cancer in *BRCA1/2* mutation carriers. Yet despite conclusive evidence that bilateral prophylactic mastectomy reduces breast cancer risk in women with *BRCA1/2* mutations by approximately 90%, the decision to undergo bilateral prophylactic mastectomy remains complex. For those women who choose bilateral prophylactic mastectomy, this study provides definitive evidence that they have chosen an effective prevention strategy.

Appendix

The appendix is included in the full-text version of this article, available on-line at www.jco.org. It is not included in the PDF (via Adobe® Acrobat Reader®) version.

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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 62:676-689, 1998

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 336:1401-1408, 1997

3. Easton DF, Narod SA, Ford D, et al: The genetic epidemiology of BRCA1. Breast Cancer Linkage Consortium. Lancet 344:761, 1994

4. Hartmann LC, Schaid DJ, Woods JE, et al: Efficacy of bilateral prophylactic mastectomy in women with a family history of breast cancer. N Engl J Med 340:77-84, 1999

5. Hartmann LC, Sellers TA, Schaid DJ, et al: Efficacy of bilateral prophylactic mastectomy in BRCA1 and BRCA2 gene mutation carriers. J Natl Cancer Inst 93:1633-1637, 2001

6. Meijers-Heijboer H, van Geel B, van Putten WL, et al: Breast cancer after prophylactic bilateral mastectomy in women with a BRCA1 or BRCA2 mutation. N Engl J Med 345:159-164, 2001

7. Rebbeck TR, Levin AM, Eisen A, et al: Breast cancer risk after bilateral prophylactic oophorectomy in BRCA1 mutation carriers. J Natl Cancer Inst 91:1475-1479, 1999

8. Brose MS, Rebbeck TR, Calzone KA, et al: Cancer risk estimates for BRCA1 mutation carriers identified in a risk evaluation program. J Natl Cancer Inst 94:1365-1372, 2002

9. Klaren HM, van't Veer LJ, van Leeuwen FE, et al: Potential for bias in studies on efficacy of prophylactic surgery for BRCA1 and BRCA2 mutation. J Natl Cancer Inst 95:941-947, 2003

10. Easton DF, Consortium TBCL: Cancer risks in BRCA2 mutation carriers. J Natl Cancer Inst 91:1310-1316, 1999

11. Thompson D, Easton DF: Cancer incidence in BRCA1 mutation carriers. J Natl Cancer Inst 94:1358-1365, 2002

12. Singletary SE: Skin-sparing mastectomy and immediate breast reconstruction. Medscape Womens Health 1:2, 1996

13. Ghosh K, Hartmann LC: Current status of prophylactic mastectomy. Oncology (Huntingt) 16:1319-1325, 2002

14. Contant CM, Menke-Pluijmers MB, Seynaeve C, et al: Clinical experience of prophylactic mastectomy followed by immediate breast reconstruction in women at hereditary risk of breast cancer (HB(O)C) or a proven BRCA1 and BRCA2 germ-line mutation. Eur J Surg Oncol 28:627-632, 2002

15. Jacobsen WM, Meland NB, Woods JE: Autologous breast reconstruction with use of transverse rectus abdominis musculocutaneous flap: Mayo Clinic experience with 147 cases. Mayo Clin Proc 69:635-640, 1994

16. Martin AM, Weber BL: Genetic and hormonal risk factors in breast cancer. J Natl Cancer Inst 92:1126-1135, 2000

17. Rebbeck TR, Lynch HT, Neuhausen SL, et al: Prophylactic oophorectomy in carriers of BRCA1 or BRCA2 mutations. N Engl J Med 346:1616-1622, 2002

18. King MC, Wieand S, Hale K, et al: Tamoxifen and breast cancer incidence among women with inherited mutations in BRCA1 and BRCA2: National Surgical Adjuvant Breast and Bowel Project (NSABP-P1) Breast Cancer Prevention Trial. JAMA 286:2251-2256, 2001

19. 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 356:1876-1881, 2000