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BREAST CANCER AFTER PROPHYLACTIC BILATERAL MASTECTOMY IN WOMEN WITH A *BRCA1* OR *BRCA2* MUTATION

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ABSTRACT

Background Women with a *BRCA1* or *BRCA2* mutation have a high risk of breast cancer and may choose to undergo prophylactic bilateral total mastectomy. We investigated the efficacy of this procedure in such women.

Methods We conducted a prospective study of 139 women with a pathogenic *BRCA1* or *BRCA2* mutation who were enrolled in a breast-cancer surveillance program at the Rotterdam Family Cancer Clinic. At the time of enrollment, none of the women had a history of breast cancer. Seventy-six of these women eventually underwent prophylactic mastectomy, and the other 63 remained under regular surveillance. The effect of mastectomy on the incidence of breast cancer was analyzed by the Cox proportional-hazards method in which mastectomy was modeled as a time-dependent covariate.

Results No cases of breast cancer were observed after prophylactic mastectomy after a mean (±SE) follow-up of 2.9±1.4 years, whereas eight breast cancers developed in women under regular surveillance after a mean follow-up of 3.0±1.5 years (P=0.003; hazard ratio, 0; 95 percent confidence interval, 0 to 0.36). The actuarial mean five-year incidence of breast cancer among all women in the surveillance group was 17±7 percent. On the basis of an exponential model, the yearly incidence of breast cancer in this group was 2.5 percent. The observed number of breast cancers in the surveillance group was consistent with the expected number (ratio of observed to expected cases, 1.2; 95 percent confidence interval, 0.4 to 3.7; P=0.80).

Conclusions In women with a *BRCA1* or *BRCA2* mutation, prophylactic bilateral total mastectomy reduces the incidence of breast cancer at three years of follow-up. (N Engl J Med 2001;345:159-64.)

THE identification of the breast-cancer–susceptibility genes *BRCA1*[1] and *BRCA2*[2] evoked widespread interest in genetic testing among women at risk for a mutation in these genes.[3,4] We found that 57 percent of women without breast cancer who had a 50 percent chance of carrying a *BRCA1* or *BRCA2* mutation requested genetic testing.[4] This result indicates the need to determine the efficacy of the various options for reducing the risk of breast cancer and for early detection in women with a *BRCA1* or *BRCA2* mutation.

Women with a *BRCA1* or *BRCA2* mutation have a cumulative lifetime risk of invasive breast cancer (up to the age of 70 years) of 55 to 85 percent and of invasive epithelial ovarian cancer of 15 to 65 percent.[5,6] In these women the risk of breast cancer begins to increase near the age of 25 years, and their overall survival once breast cancer does develop is similar to that of age-matched patients with sporadic cases of breast cancer: in both, the 10-year survival rate is about 50 percent.[7,8]

Current risk-reduction strategies for women with a *BRCA1* or *BRCA2* mutation include regular surveillance; prophylactic mastectomy, oophorectomy, or both; and chemoprevention.[9-11] In our experience, 50 percent of women who have a *BRCA1* or *BRCA2* mutation have chosen to undergo prophylactic bilateral mastectomy.[4] Until now, however, there have been only retrospective studies of the efficacy of the procedure in women with an increased risk of breast can-

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cer on the basis of the family pedigree and not DNA testing.[12]

We investigated the efficacy of prophylactic mastectomy in women with a proven pathogenic *BRCA1* or *BRCA2* mutation. Because a randomized trial is impossible for ethical reasons, we performed a prospective cohort study of women at a single institution who chose either prophylactic mastectomy or regular surveillance.

METHODS

Study Subjects

Beginning on January 1, 1992, we studied all women with a *BRCA1* or *BRCA2* mutation who were being monitored for breast cancer because of familial clustering of breast cancer, ovarian cancer, or both at the Daniel den Hoed Cancer Center in Rotterdam, the Netherlands. We included all women who had been given a molecular diagnosis before January 1, 2000. Women with a *BRCA1* or *BRCA2* mutation in whom breast cancer developed before January 1, 1992, and one woman in whom breast cancer was detected at the first screening were excluded. The date January 1, 1992, was chosen because at that time, a multidisciplinary team at our family cancer clinic took over the care of women at high risk for breast cancer. A total of 139 women fulfilled the criteria. Eventually, 76 of these women chose to undergo prophylactic bilateral mastectomy before the end of the follow-up period (March 1, 2001), whereas the other 63 women chose to remain under regular surveillance. In all but two women prophylactic mastectomy was performed after the molecular diagnosis was established.

Data Collection and Follow-up

Information on vital status and the occurrence of cancer was extracted from the women's medical files. All women were regularly monitored at our clinic until March 1, 2001, and were enrolled in clinical research programs approved by our medical ethics committee (protocol DDHK 91-17, updated in 1995). We obtained pathology reports of all mastectomy specimens and of all breast-biopsy specimens from the women who were being monitored. Information on oophorectomy performed for any reason (mostly at our clinic) was obtained from the women themselves and was verified by a review of all medical records. Premenopausal oophorectomy was defined as bilateral oophorectomy before the age of 56 years and was performed prophylactically in the case of 59 women, for benign disease in the case of 1 woman, for ovarian cancer in the case of 7 women, and for cervical cancer in the case of 1 woman (Table 1). No women were lost to follow-up after prophylactic mastectomy. Of the women in the surveillance group, three died of ovarian cancer and two chose to be monitored at another hospital for practical reasons.

Surgical Techniques and Surveillance

In all cases a standard, bilateral, simple total mastectomy (including the nipple) was performed by a surgical oncologist at the Daniel den Hoed Cancer Center. In 74 of the 76 women, the breasts were reconstructed with silicone prostheses by a plastic surgeon in the same session, followed later by a nipple reconstruction.

According to national guidelines, regular surveillance for breast cancer consists of a monthly breast self-examination, a clinical breast examination every six months, and yearly mammography. Since 1995, magnetic resonance imaging (MRI) has been an option at our clinic for women with mammographically very dense tissue and those with a *BRCA1* or *BRCA2* mutation. When indicated, ultrasonography with or without fine-needle aspiration was also performed. The age at entry into the surveillance program was generally 25 years or younger in women with relatives in whom breast cancer had been diagnosed before the age of 30 years.

To rule out overt breast cancer at the time of prophylactic mastectomy, any or all of the following were performed no more than three months before surgery: a physical examination of the breast, mammography, or MRI. After prophylactic mastectomy, the chest wall and regional lymph nodes were examined every six months. In most women, computed tomography of the chest was performed one year after prophylactic mastectomy.

TABLE 1. CHARACTERISTICS OF THE WOMEN.*

CHARACTERISTIC	MASTECTOMY GROUP (N=76)	SURVEILLANCE GROUP (N=63)	P VALUE
Age at entry†			0.42
Mean — yr	37.7±7.7	39.5±11.5	
Median — yr	35.8	39.9	
Range — yr	23–58	19–64	
<30 yr — no. (%)	11 (14)	17 (27)	
30–39 yr — no. (%)	39 (51)	17 (27)	
40–49 yr — no. (%)	18 (24)	16 (25)	
≥50 yr — no. (%)	8 (11)	13 (21)	
Premenopausal oophorectomy — no. (%)	44 (58)	24 (38)	0.03
For gynecologic cancer	2	6	
For benign gynecologic disease	1	0	
Prophylaxis	41	18	
Duration of follow-up after prophylactic mastectomy or start of surveillance			0.87
Mean — yr	2.9±1.4	3.0±1.5	
Median — yr	2.8	2.7	
Range — yr	0.1–6.5	0.4–8.3	
No. of woman-yr	219	190	
Duration of surveillance before prophylactic mastectomy			
Median — yr	1.3	—	
Range — yr	0.1–5.7	—	
No. of woman-yr	128	—	
Mutations — no. (%)			0.42
BRCA1	64 (84)	56 (89)	
BRCA2	12 (16)	7 (11)	
No. of cases of breast cancer after study entry	0	8	

*Plus–minus values are means ±SE. Premenopausal oophorectomy was defined as bilateral oophorectomy before the age of 56 years.

†The age at entry in the mastectomy group is based on the date of prophylactic mastectomy, and the age at entry in the surveillance group is based on the date on which surveillance was initiated.

Analysis of *BRCA1* and *BRCA2* Mutations and Histologic Examination

DNA analysis was performed according to standard procedures.[13-15] *BRCA1* and *BRCA2* linkage analysis was used until 1994 and 1995, respectively, to identify the presence of hereditary breast cancer; from 1994 to 2000 we used direct mutation analysis. All *BRCA1* and *BRCA2* mutations were pathogenic, since they resulted in a premature truncation of the BRCA1 or BRCA2 protein.

Mastectomy specimens were examined histologically to rule out the presence of occult breast cancer. From each quadrant of the specimen, microscopical sections from three random blocks were examined according to standard procedures.

Statistical Analysis

We used a chi-square test and a t-test to compare the characteristics of the group of 76 women who chose to undergo mastectomy with those of the 63 women who opted to continue being monitored. We used a Cox proportional-hazards model to analyze the effect of prophylactic mastectomy on the incidence of breast cancer, with prophylactic mastectomy included as a time-dependent covar-

iate. To adjust for the potential effect of a change in menopausal status, either through premenopausal oophorectomy or through natural menopause (defined as occurring at the age of 56 years), we included menopausal status in the model as a time-dependent covariate. The women were followed from January 1, 1992, or from the time of the first visit after that date at our clinic until the occurrence of breast cancer or death, the end of follow-up at our clinic, or the end of the study (March 1, 2001). We determined the number of woman-years at risk for breast cancer in various age cohorts in the two groups; in this analysis we included in the surveillance-group data the number of years of surveillance in the women in the mastectomy group before prophylactic mastectomy was performed. The numbers of woman-years at risk were used to calculate the numbers of breast cancers expected on the basis of published estimates for women with a *BRCA1* mutation.[16] We calculated 95 percent confidence intervals assuming a Poisson distribution. We used the method of Kaplan and Meier to calculate the actuarial probability of breast cancer during the surveillance period. We compared these probabilities with the cumulative incidence, assuming that the model was an exponential one with a constant hazard rate, in order to have more stable estimates with longer follow-up.

A two-sided P value of less than 0.05 was considered to indicate statistical significance. All analyses were performed with the use of SPSS and Stata software.

RESULTS

Characteristics of the Women

Table 1 lists the general characteristics of the women who chose to undergo prophylactic mastectomy and those who opted for surveillance. Significantly more women in the mastectomy group than in the surveillance group had undergone a premenopausal oophorectomy (44 vs. 24 [58 percent vs. 38 percent], P=0.03). All gynecologic cancers occurred before the age of 56 years; the two such cases in the mastectomy group were ovarian cancer, stage IC. There were no significant differences between the two groups with respect to age, average duration of follow-up after entry into the study, follow-up after premenopausal oophorectomy, and type of mutation. The 26 distinct mutations — 23 in *BRCA1* and 3 in *BRCA2* — were distributed in a similar fashion in the two groups. The 139 women were from a total of 70 families; the number of women from each family ranged from 1 to 5.

The mean (±SE) duration of follow-up was 2.9±1.4 years (219 woman-years) in the mastectomy group and 3.0±1.5 years (190 woman-years) in the surveillance group (Table 1). The total number of woman-years of surveillance increased from 190 to 318 when the 128 woman-years of surveillance before prophylactic mastectomy was added.

Incidence of Breast Cancer

After prophylactic mastectomy no case of invasive breast cancer was observed in any of the 76 women during 219 woman-years at risk (Fig. 1). In the surveillance group eight invasive breast cancers were detected during 318 woman-years at risk, for a yearly incidence of 2.5 percent. The ratio of observed cases to expected cases was 1.2 (8 vs. 6.7; 95 percent confidence interval,

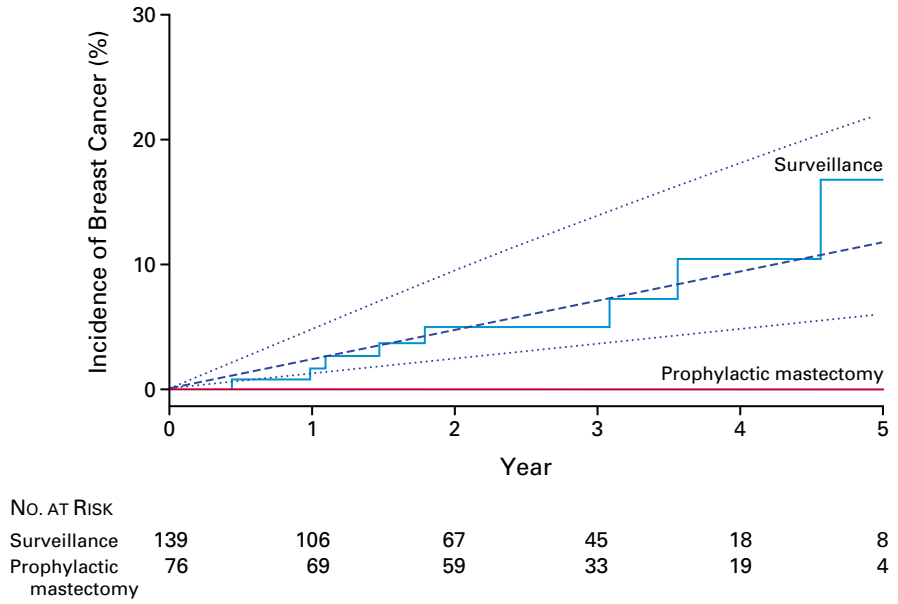

Figure 1. Actuarial Incidence of Breast Cancer among Women with a *BRCA1* or *BRCA2* Mutation after Prophylactic Mastectomy or during Surveillance.

The surveillance group includes data obtained before prophylactic mastectomy in 76 of the 139 women. The dashed line represents the probability of breast cancer during surveillance, and the dotted lines the 95 percent confidence interval. Values were calculated with the use of an exponential model in which the hazard rate was assumed to be constant.

0.4 to 3.7; P=0.80). All the affected women were from different families. The actuarial mean five-year incidence of breast cancer in the women in the surveillance group (Fig. 1) was 17±7 percent, but the number of women at risk at five years was only eight. To obtain a more stable estimate with longer periods of follow-up, we calculated cumulative incidence probabilities with the use of an exponential model in which the hazard rate was assumed to be constant. According to this model, the yearly incidence of breast cancer was 2.5 percent and the five-year cumulative incidence was 12 percent (95 percent confidence interval, 6 to 23 percent) (Fig. 1). Disregarding the years of surveillance before prophylactic mastectomy and thus restricting the actuarial analysis to the 63 women in the surveillance group, we estimated that the five-year risk of breast cancer was 24±9 percent.

Cox proportional-hazards analysis showed that mastectomy significantly (P=0.003) decreased the incidence of breast cancer (hazard ratio, 0; 95 percent confidence interval, 0 to 0.36). After adjustment for the change in menopausal status, the protective effect of mastectomy remained statistically significant (P=0.01).

Outcome in the Women with Breast Cancer

None of the eight patients in the surveillance group in whom breast cancer developed had been scheduled to undergo prophylactic mastectomy at the time of the diagnosis. The characteristics of the women and the tumors are described in Tables 2 and 3, respectively. Patients 7 and 8 underwent bilateral oophorectomy 14 and 12 months, respectively, before the diagnosis of breast cancer. Of the eight cancers, four (in Patients 1, 2, 4, and 6) were detected between screening sessions (so-called interval cancers). In these four patients the interval from screening to diagnosis was two to five months. The cancers in the other four patients (Patients 3, 5, 7, and 8) were detected during a screening session. Patient 1 became symptomatic eight weeks after her first clinical breast-cancer screening, the results of which were negative. In four of the eight patients, breast cancer was detected before the molecular diagnosis was made.

Histologic Findings in the Mastectomy Group

Invasive cancer was not detected in any of the specimens obtained at the time of prophylactic mastectomy. One 44-year-old woman with a *BRCA1* mutation had lobular carcinoma in situ.

DISCUSSION

In this prospective study we assessed the incidence of breast cancer in 139 women with a *BRCA1* or *BRCA2* mutation who chose to undergo either prophylactic mastectomy or regular surveillance. Whereas breast cancer developed in 8 of 63 women in the surveillance group, no cases of breast cancer occurred among the 76 women who underwent prophylactic mastectomy. The observed number of breast cancers in the group under surveillance is compatible with the reported incidence of breast cancer in women with a *BRCA1* or *BRCA2* mutation.[16] As compared with the incidence in the surveillance group, the incidence of breast cancer in the prophylactic-mastectomy group was significantly reduced (P=0.003), but the mean follow-up of three years calls for a cautious interpretation of our results.

TABLE 2. CHARACTERISTICS OF THE EIGHT WOMEN IN THE SURVEILLANCE GROUP IN WHOM BREAST CANCER DEVELOPED.

PATIENT NO.	AGE AT DIAGNOSIS	MUTATION	PRIOR OOPHORECTOMY	FOLLOW-UP AFTER DIAGNOSIS	CURRENT STATUS*
	yr			mo	
1	23	4284delAG in *BRCA1*	No	15	NED
2	28	IVS12–1643del3835 in *BRCA1* (a 3.8-kb deletion affecting exon 13)	No	41	Died of breast cancer
3	39	4284delAG in *BRCA1*	No	18	NED
4	39	2804delAA in *BRCA1*	No	33	NED
5	43	IVS12–1643del3835 in *BRCA1* (a 3.8-kb deletion affecting exon 13)	No	97	NED
6	44	1129delA in *BRCA1*	No	25	NED
7	49	3668delA+G3669 in *BRCA1*	Yes	14	NED
8	53	IVS21–36del510 in *BRCA1* (a 510-bp deletion affecting exon 22)	Yes	19	NED

*NED denotes no evidence of disease.

TABLE 3. CHARACTERISTICS OF THE TUMORS IN THE EIGHT WOMEN IN THE SURVEILLANCE GROUP IN WHOM BREAST CANCER DEVELOPED.

PATIENT NO.	TUMOR SIZE	NO. OF POSITIVE NODES/ TOTAL NO. ASSESSED	HISTOLOGIC TYPE	GRADE	ESTROGEN- AND PROGESTERONE-RECEPTOR STATUS	INTERVAL FROM START OF SURVEILLANCE TO DIAGNOSIS	FINDINGS*			
							BSE	CBE	MAMMOGRAPHY	MRI
	mm					mo				
1	25, 13	1/15	Ductal	III	Negative	2	SC	SC	PB	SC
2	40	2/13	Ductal	III	Negative	12	SC	SC	PB	ND
3	18	0/1 sentinel node	Ductal	III	Negative	31	NA	SC	NA	SC
4	7	3/21	Ductal	III	Negative	10	SC	SC	SC	ND
5	20	6/18	Ductal	III	Negative	23	NA	SC	PB	SC
6	12	0/19	Ductal	III	Negative	35	SC	SC	PB	SC
7	10	0/1 sentinel node	Ductal	II	Negative	42	NA	NA	NA	SC
8	15	0/1 sentinel node	Ductal	III	Positive	22	NA	NA	SC	SC

*BSE denotes breast self-examination, CBE clinical breast examination, MRI magnetic resonance imaging, SC suspicion of cancer, PB high probability of a benign lesion, ND not done, and NA no abnormalities.

Until now, only retrospective studies of the outcome of prophylactic mastectomy (mainly subcutaneous, and thus often incomplete) have been published.[12] Hartmann et al.[17] reported the results of prophylactic bilateral mastectomy in 639 women with a family history of breast cancer; at least 12 of these women had a *BRCA1* or *BRCA2* mutation.[18] After a median follow-up of 14 years, there was an approximate 90 percent reduction in the risk of breast cancer; the risk of death was also reduced significantly. All seven breast cancers occurred after subcutaneous bilateral mastectomy; there were none after total mastectomy.[17] Moreover, breast cancer did not develop in any of the women with a confirmed *BRCA1* or *BRCA2* mutation after a median follow-up of 16 years,[18] which leads us to anticipate that prophylactic mastectomy will reduce the long-term risk of breast cancer in the women with a *BRCA1* or *BRCA2* mutation whom we studied.

It is uncertain whether mammographic surveillance of premenopausal women with a *BRCA1* or *BRCA2* mutation contributes substantially to early detection of breast cancer.[19] Considering the women's young age in our study cohort and the stage and pathological characteristics of their breast cancers at diagnosis, we estimate that 35 to 50 percent of women under surveillance in whom primary breast cancer develops will die of distant metastasis within 10 to 15 years.[7,8] Assuming that within 10 years breast cancer will develop in approximately 25 percent of the women undergoing regular surveillance, we estimate that 10 to 20 percent of women who choose surveillance will die of breast cancer within 20 years. During the three years of follow-up in our study, there was one death due to breast cancer (Table 2).

Currently, several large, prospective studies are investigating whether MRI screening adds to the efficacy of mammographic screening in women at high risk for breast cancer.[20,21] In our study MRI was performed in six women at the time of diagnosis and detected all six cancers, but mammography was diagnostic in only two of the eight women with breast cancer. In view of the high number of interval cancers (four of eight), the use of high-resolution imaging and more frequent screening might be useful in women with a *BRCA1* or *BRCA2* mutation.

There is little in the literature on the histologic findings in specimens obtained at the time of prophylactic mastectomy from women with a *BRCA1* or *BRCA2* mutation. In two studies, in about 35 percent of unaffected high-risk women, proliferative breast disease (marked or atypical hyperplasia) was found in the surgical specimens.[22,23] This abnormality was found in specimens from only 13 percent of women with an average risk of breast cancer.[23] In two women with a strong family history of breast cancer, microcalcifications and invasive breast cancer were detected within one year after the finding of proliferative disease.[23] In contralateral specimens obtained at the time of prophylactic mastectomy from women with prior breast cancer and either a genetic risk or a family history of breast cancer, a higher prevalence of malignant lesions was observed.[9,22] In our study, there was one carcinoma in situ and several prophylactic-mastectomy specimens with various degrees of hyperplasia and atypia. However, we cannot exclude the possibility that small invasive tumors were overlooked.

In our study all eight breast cancers occurred in women with a *BRCA1* mutation. This finding may be partly explained by the fact that only about 10 percent of the woman-years of surveillance were accounted for by women with *BRCA2* mutations.

Apart from surveillance and prophylactic mastec-

tomy, women with a *BRCA1* or *BRCA2* mutation may choose to undergo bilateral oophorectomy before menopause, chemoprevention, or both to reduce the risk of breast cancer. Such interventions may reduce the risk of breast cancer by about 50 percent,[24-26] but the use of tamoxifen as a preventive agent has been questioned in view of its long-term side effects.[27]

Prophylactic mastectomy is a highly personal decision. In counseling high-risk women, the protective effect of prophylactic mastectomy must be weighed against possible surgical complications and psychological problems. Up to 30 percent of the women who undergo the procedure will have surgical complications, depending on the type of surgery and the length of follow-up.[12,28] A long-term study of prophylactic mastectomy reported unanticipated repeated operations in 49 percent of women,[29] but these results may not be applicable to prophylactic mastectomies as they are currently performed. Psychological studies of women who had undergone a prophylactic mastectomy did not find that, overall, the procedure had detrimental effects on body image and sexuality.[30-33]

In conclusion, our data and those of Hartmann et al.[17,18] indicate that prophylactic bilateral total mastectomy substantially reduces the incidence of breast cancer among women with a *BRCA1* or *BRCA2* mutation. Nevertheless, longer follow-up and studies of more patients are required to establish the protective effect and determine the long-term complications of this procedure.

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