Hormone Therapy and the Risk of Breast Cancer in *BRCA1* Mutation Carriers

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Background Hormone therapy (HT) is commonly given to women to alleviate the climacteric symptoms associated with menopause. There is concern that this treatment may increase the risk of breast cancer. The potential association of HT and breast cancer risk is of particular interest to women who carry a mutation in *BRCA1* because they face a high lifetime risk of breast cancer and because many of these women take HT after undergoing prophylactic surgical oophorectomy at a young age.

Methods We conducted a matched case–control study of 472 postmenopausal women with a *BRCA1* mutation to examine whether or not the use of HT is associated with subsequent risk of breast cancer. Breast cancer case patients and control subjects were matched with respect to age, age at menopause, and type of menopause (surgical or natural). Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated with conditional logistic regression. Statistical tests were two-sided.

Results In this group of *BRCA1* mutation carriers, the adjusted OR for breast cancer associated with ever use of HT compared with never use was 0.58 (95% CI = 0.35 to 0.96; $P = .03$). In analyses by type of HT, an inverse association with breast cancer risk was observed with use of estrogen only (OR = 0.51, 95% CI = 0.27 to 0.98; $P = .04$); the association with use of estrogen plus progesterone was not statistically significant (OR = 0.66, 95% CI = 0.34 to 1.27; $P = .21$).

Conclusion Among postmenopausal women with a *BRCA1* mutation, HT use was not associated with increased risk of breast cancer; indeed, in this population, it was associated with a decreased risk.

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Approximately 3% of invasive breast cancers can be attributed to a mutation in *BRCA1* or *BRCA2* (1). Women who carry a *BRCA1* mutation face a lifetime risk of breast cancer of 60%–80% (2,3), but the risk can be reduced substantially by performing surgical oophorectomy before menopause (4). Because the observed reduction in risk is believed to be due to the withdrawal of ovarian hormones, concern has been raised that administration of exogenous hormones in the form of hormone therapy (HT) given to help alleviate the climacteric symptoms associated with menopause may increase the risk of breast cancer, either in women undergoing surgical oophorectomy or in women following natural menopause. The majority of HT preparations contain estrogen, but not all contain progesterone. In the Women's Health Initiative randomized trial, a statistically significant increase in the risk of breast cancer was seen in association with the use of combined therapy (estrogen plus progesterone) but not with estrogen alone (5–8). One study has been conducted in *BRCA1* mutation carriers; Rebbeck et al. (9)

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CONTEXT AND CAVEATS

Prior knowledge

Use of hormone therapy (HT) after menopause may increase the risk of breast cancer in the general population. The effects of HT in women with mutations in the *BRCA1* gene, however, are not known.

Study design

Case–control study of postmenopausal women who carry a *BRCA1* mutation to compare the risks of breast cancer among those who used HT and those who did not.

Contribution

In this study of *BRCA1* mutation carriers, a decrease in breast cancer risk was observed among those who took HT compared with those who did not.

Implications

HT use does not appear to be associated with an increased risk for breast cancer among postmenopausal women who carry a *BRCA1* mutation. Indeed, in this study, it was associated with a decreased risk among such women.

Limitations

The study was relatively small, women who had undergone preventive mastectomy or used tamoxifen were excluded, and the results depended on the participants' recall of HT use. An average of approximately 5.6 years had elapsed between breast cancer diagnosis and the completion of the questionnaire, so if *BRCA1* mutation carriers who previously took HT have shorter survival after breast cancer diagnosis than those who did not take HT, this would have skewed the results in the negative direction that was observed.

From the Editors

found inverse associations between oophorectomy and breast cancer risk among women who did and who did not use HT. However, that study (9) included both pre- and postmenopausal women, and the authors did not directly compare the risks of breast cancer in postmenopausal women who did and did not take HT. We carried out a case–control study of *BRCA1* mutation carriers that was restricted to postmenopausal women, and we examined whether or not the use of HT following surgical or natural menopause is associated with the subsequent risk of breast cancer.

Subjects and Methods

Study Population and Data Collection

Eligible study subjects were identified from a cohort of living women from one of 55 participating centers in nine countries who were participants in ongoing clinical research protocols at the host institutions. All study subjects (with the exception of those from the University of Utah) received genetic counseling and provided written informed consent for genetic testing. In most cases, testing was initially offered to women who had been affected with breast or ovarian cancer. When a *BRCA1* or *BRCA2* mutation was identified in a proband or a relative, genetic testing was offered to other at-risk women in the family. Mutation detection was performed using a range of techniques, but all nucleotide sequences were confirmed by direct sequencing of DNA. A woman was eligible for the cohort when molecular analysis established that she was a carrier of a deleterious mutation in *BRCA1* or *BRCA2*. Most (>95%) of the mutations identified in the study subjects were nonsense mutations or small deletions, insertions, or frameshifts. The cohort was established in 1995 as part of a prospective study designed to evaluate nongenetic modifiers of cancer risk in *BRCA1* and *BRCA2* mutation carriers, such as HT and oral contraceptives. Data on oral contraceptive use and breast cancer and ovarian cancer risk in this population have been published previously (10,11). The institutional review boards of the host institutions approved the study.

A questionnaire was administered to each woman in the cohort at the time of a clinic appointment or at their home at a later date. In some centers, questionnaires were mailed to the study subjects. Variables of interest included information on demography and ethnic group. Information was requested from the study centers on the estrogen receptor (ER) status of the tumors of the case patients; however, ER status was available for only 44% of the case patients. The questionnaire included questions about the women's medical and reproductive histories and selected lifestyle factors, including past and current use of HT. The subjects were asked if they had ever taken HT, what year they began using HT, what year they stopped using HT, the total duration of HT use, and whether they currently used HT. Information about the type of HT was also requested.

Subjects for the current study were drawn from the 6062 women within the cohort with a *BRCA1* mutation. In total, 2415 women had reached menopause without a diagnosis of breast cancer. Of these, we excluded 349 women because we could not determine their menopausal status (eg, hysterectomy without oophorectomy) or because data were missing on key variables related to menopause. Data were missing on HT for 67 women, and these women were also excluded. This group of 67 included 45 women who reported having used HT in the past but could not recall the name of the drug. A total of 37 women who reported having used HT before menopause were also excluded. We excluded 1010 women who had been diagnosed with ovarian, fallopian, peritoneal, or omental cancer and 15 women who were diagnosed with another form of cancer. We excluded 99 women who underwent bilateral preventive mastectomy and 17 women who took tamoxifen for prophylaxis. After these exclusions, there remained 821 postmenopausal women who were eligible for the study, including 304 women with breast cancer (potential case patients) and 517 women without breast cancer (potential control subjects). The potential case patients had been diagnosed with invasive cancer of the breast after reaching menopause (ie, in the year before menopause or thereafter). They had been diagnosed before the completion of the questionnaire (median year of diagnosis 1997; range = 1959–2005). The diagnosis of breast cancer was confirmed at the time the case patient underwent genetic testing at the collaborating center. Control subjects had also undergone menopause but did not subsequently develop breast cancer. A single control subject was selected for each case patient, matched according to year of birth (within 2 years), age at menopause (within 2 years), and type of menopause (surgical vs natural). A total of 236 matched sets were generated.

Statistical Analysis

A matched case–control analysis was performed. McNemar test was used to test for differences in categorical variables with two

categories. If there were more than two categories, then the marginal homogeneity test was used. The univariate odds ratios (ORs) and 95% confidence intervals (CIs) for breast cancer associated with HT use were estimated using conditional logistic regression for matched sets. We considered HT use only in the years before diagnosis of breast cancer in the case patients; that is, a control subject who first used HT after the age of diagnosis of her matched case patient was considered to be unexposed. We conducted a subanalysis to evaluate the relationship of current use (vs past or never use) with the risk of breast cancer. We also evaluated the association with duration of use; subjects were divided into those who used HT for 3 years or less vs more than 3 years (roughly the median duration of use among control subjects). HT preparations were divided into those containing estrogen only or estrogen and progesterone. Only three women took progesterone-only HT, and they were excluded from the subgroup analysis. A multivariable analysis was carried out to control for the potential confounding effects of oral contraceptive use, parity, and country of residence. Oral contraceptive use was coded as ever or never use, and parity was coded as zero, one, two, or three or more births. Data were analyzed separately for women with natural and surgical menopause and for both groups combined. All statistical tests were two-sided. All analyses were performed using the SAS statistical package, version 9.1.3 (SAS Institute, Cary, NC). *P* values less than .05 were considered as statistically significant.

Results

We identified a total of 236 matched pairs of *BRCA1* mutation carriers. The breast cancer case patients and control subjects were similar with respect to date of birth, age at menopause, age and year at interview, oral contraceptive use, smoking status, and parity (Table 1). Case patients and control subjects were matched on both age at menopause and type of menopause; this strategy was successful in generating groups of case patients and control subjects who were similar in terms of their menopausal histories, family histories, and other demographic factors. Most (74%) of the case patients and control subjects had undergone natural menopause.

We examined the relationship between HT use and the risk of breast cancer in *BRCA1* mutation carriers (Tables 1 and 2). A higher proportion of control subjects than case patients had used HT at some time (29% vs 20%), and the difference was statistically significant ($P = .02$). Among women who ever used HT, the average duration of HT use was similar for the case patients (4.0 years) and the control subjects (3.7 years) ($P = .7$).

A multivariable analysis was conducted, adjusting for parity, oral contraceptive use, and country of origin. Compared with those who had never used HT, women who had used HT had a lower risk of breast cancer (OR = 0.58%, 95% CI = 0.35 to 0.96; $P = .03$) (Table 2). The OR estimates were similar in the subgroups

Table 1. Characteristics of case patients and control subjects

Variables	Control subjects (n = 236)	Case patients (n = 236)	P*
Year of birth, mean	1943	1943	
Age at interview (range), y	58.2 (32–85)	58.2 (34–81)	.71
Year of interview (range)	2001 (1991–2006)	2001 (1988–2007)	.55
Age at diagnosis (range), y	NA	52.6 (30–80)	
Menopause type, No. (%)			
Natural	174 (74)	174 (74)	
Surgical	62 (26)	74 (26)	
Age at menopause (range), y	47.2 (28–58)	46.9 (28–57)	
Natural	48.8 (38–58)	48.5 (40–57)	
Surgical	42.6 (28–52)	42.3 (28–52)	
Hormone therapy use, No. (%)	68 (29)	47 (20)	.02
Mean duration, y, users	3.7	4.0	.70
Mean duration, y, all	1.1	0.8	.23
Oral contraceptive use, ever, No. (%)	102 (43)	95 (41)	.70
Smoker, ever, No. (%)	107 (48)	112 (49)	.85
Nulliparous, No. (%)	22 (9)	20 (9)	.87
Mean parity	2.5	2.5	.57
Mean no. of first-degree relatives with breast cancer	0.8	0.9	.36
Country of residence, No. (%)			.50
Israel	13 (6)	15 (6)	
Poland	80 (34)	96 (41)	
United States	57 (24)	52 (22)	
Canada	40 (17)	37 (16)	
Other Europe (Italy, Norway, United Kingdom, Sweden, and The Netherlands)	46 (20)	36 (15)	.65
Ethnic group, No. (%)			.50
Other white	233 (82)	183 (78)	
Jewish	53 (14)	40 (17)	
French Canadian	15 (3)	10 (4)	
Other	2 (1)	3 (1)	

* *P* values (two-sided) were calculated using paired *t* test for continuous variables or McNemar test for categorical variables. *P* values were not calculated for variables used for matching (ie, age at menopause and type of menopause). NA = not applicable.

Table 2. Risk of breast cancer with HT use by type of menopause*

Type of menopause	Control subjects, No.	Case patients, No.	OR (95% CI) Unadjusted	*P*	Multivariable	*P*
Surgical (62 pairs)						
No HT	28	39	1 (referent)		1.0 (referent)	
HT	34	23	0.43 (0.18 to 0.96)	.04	0.48 (0.19 to 1.21)	.12
Natural (174 pairs)						
No HT	140	34	1 (referent)		1.0 (referent)	
HT	150	24	0.67 (0.38 to 1.17)	.16	0.68 (0.37 to 1.27)	.22
All (236 pairs)						
No HT	168	189	1.0 (referent)		1.0 (referent)	
HT	68	47	0.57 (0.39 to 0.91)	.02	0.58 (0.35 to 0.96)	.03

* Multivariable ORs were adjusted for parity (0, 1, 2, or ≥3), oral contraceptive use (never vs ever), and country of residence. *P* values (two-sided) were calculated using conditional logistic regression. HT = hormone therapy; OR = odds ratio; CI = confidence interval.

of *BRCA1* mutation carriers who had undergone surgical (OR = 0.48, 95% CI = 0.19 to 1.21) and natural (OR = 0.68, 95% CI = 0.37 to 1.27) menopause; however, the former category was small (n = 62 pairs), and neither association was statistically significant in the multivariable analysis (Table 2).

We evaluated the association between HT and breast cancer risk in subgroups defined by duration and timing of use and type of HT preparation. The OR did not depend on the age at diagnosis or the age at menopause (Table 3). There was no apparent modification of the OR with duration of use (Table 4), and the association was similar for current users and past users (Table 4). The association was similar for women who used estrogen alone and those who used combined therapy (Table 5).

Information was available regarding ER status for 103 case patients (44%). If HT were a risk factor for ER-positive breast cancer but not ER-negative breast cancer, then we would expect previous HT use to be greater among women with ER-positive breast cancers than among women with ER-negative breast cancers. This was not the case; HT use was reported for 12% (4 of 33) patients with ER-positive tumors and for 23% of patients (16 of 70) with ER-negative tumors (*P* = .29).

Discussion

These findings suggest that the use of HT is not associated with an increase in the risk of breast cancer among women with a *BRCA1* mutation. We were interested in examining HT use and breast cancer risk in *BRCA1* mutation carriers because oophorectomy has become a standard of care in North America and Western Europe for preventing cancer in women with a *BRCA1* or *BRCA2* mutation. Currently, after receiving a positive genetic test result, 68% of women in the United States and 54% of women in Canada with a *BRCA1* or *BRCA2* mutation undergo oophorectomy (12). The surgery has been associated with risk reductions of 50% or more for breast cancer (4) and of 80% for ovarian or peritoneal cancer (13). Some women might be reluctant to undergo premenopausal oophorectomy because of the effects of surgical menopause and are concerned that if HT were taken to alleviate symptoms, then their risk of breast cancer might rise.

We observed an OR below unity, indicative of an inverse association between HT use and breast cancer risk. The magnitude of the association appeared to be as great, or even greater, for women after surgical menopause than it was for women after natural menopause. This information should be reassuring to women who wish

Table 3. Risk of breast cancer with HT use by age at menopause and age at diagnosis*

Variable	Control subjects, No.	Case patients, No.	OR (95% CI) Univariate	*P*	Multivariable	*P*
Age at menopause						
≤45 y						
No HT	46	57	1 (referent)		1 (referent)	
HT	32	21	0.52 (0.26 to 1.05)	.07	0.50 (0.23 to 1.10)	.08
>45 y						
No HT	122	132	1 (referent)		1 (referent)	
HT	36	26	0.62 (0.33 to 1.15)	.13	0.62 (0.32 to 1.21)	.16
Age at diagnosis						
≤50 y						
No HT	52	63	1 (referent)		1 (referent)	
HT	32	21	0.50 (0.24 to 1.03)	.06	0.49 (0.23 to 1.04)	.06
>50 y						
No HT	116	126	1 (referent)		1 (referent)	
HT	36	26	0.63 (0.34 to 1.16)	.14	0.63 (0.34 to 1.16)	.22

* Multivariable ORs adjusted for parity (0, 1, 2, or ≥3), oral contraceptive use (never vs ever), and country of residence. *P* values (two-sided) were calculated using conditional logistic regression. HT = hormone therapy; OR = odds ratio; CI = confidence interval.

Table 4. Risk of breast cancer by duration and time of HT use*

Variable	Control subjects, No.	Case patients, No.	OR (95% CI) Univariate	*P*	Multivariable	*P*
Duration of HT, y						
No HT	168	189	1 (referent)		1 (referent)	
HT ≤3	41	31	0.61 (0.34 to 1.12)	.11	0.63 (0.34 to 1.16)	.14
HT >3	27	16	0.52 (0.26 to 1.02)	.06	0.51 (0.24 to 1.08)	.08
Time of use						
Never	168	189	1 (referent)		1 (referent)	
Current use	51	39	0.64 (0.39 to 1.07)	.09	0.63 (0.37 to 1.07)	.09
Past use	17	8	0.43 (0.14 to 0.94)	.04	0.43 (0.16 to 1.17)	.10

* Multivariable ORs adjusted for parity (0, 1, 2, or ≥3), oral contraceptive use (never vs ever), and country of residence. *P* values (two-sided) were calculated using conditional logistic regression. HT = hormone therapy; OR = odds ratio; CI = confidence interval.

to undergo preventive oophorectomy before menopause, but it needs to be confirmed in subsequent studies. Premenopausal women face a greater residual risk of breast cancer than do women who have entered menopause; for them, the net reduction in breast cancer risk associated with oophorectomy is substantial (4). In the noncarrier population, the increased breast cancer risk associated with HT appears to be stronger for ER-positive cancers than ER-negative cancers (14). If HT were a risk factor for ER-positive breast cancer in *BRCA1* mutation carriers as well, we would have expected that a greater proportion of women with ER-positive breast cancers had used HT than women with ER-negative breast cancers. This was not seen, but because we were able to obtain ER status for only about one-half of the breast cancer patients, the numbers are too small to draw a definite conclusion.

In this study, neither use of estrogen alone nor use of estrogen combined with progesterone was associated with an increase in breast cancer risk among *BRCA1* mutation carriers. This observation is in contrast to the situation in the general (ie, noncarrier) population, in which formulations containing both estrogen and progesterone have been associated with a substantial increase in breast cancer risk. For example, in the Women's Health Initiative randomized trial, a hazard ratio (HR) of 1.3 (95% CI = 1.0 to 1.6) was reported for breast cancer in association with use of estrogen plus progesterone (5,6), and an HR of 0.8 (95% CI = 0.6 to 1.0) was reported for estrogen alone (7,8). In the Million Women Study (15), an HR of 2.0 (95% CI = 1.9 to 2.1) was associated with current use of estrogen plus progesterone, and an HR of 1.3 (95% CI = 1.2 to 2.4) was associated with current use of estrogen alone.

The increase in breast cancer risk in the Million Women Study was restricted to current HT users; after treatment stopped, the risk dissipated rapidly. A rapid and reversible effect might be seen if HT accelerated the growth of existing ER-positive tumors or preneoplastic lesions. The majority of *BRCA1*-associated breast cancers in our study (68%) were ER negative; if the adverse effect of HT were limited to ER-positive cancers, then we would not expect to see an acute effect of similar magnitude in mutation carriers. It may be also that HT use protects against the early stages of cancer development, which results in a decline in the incidence of breast cancer later in life. The Women's Health Initiative randomized trial (5–8) measured the combined effect of past and current use of estrogen on breast cancer risk; the OR for estrogen alone was borderline protective (OR = 0.77, 95% CI = 0.59 to 1.01). It has been proposed that the rapid decline in breast cancer risk seen in the United States in 2003 is the consequence of a drop in HT usage in the preceding years (14). The decline in incidence was most pronounced for ER-positive tumors, favoring the hypothesis that the use of HT is associated with a rapid but reversible increase in the risk of ER-positive breast cancers. If HT promotes the growth of existing ER-positive breast cancers but protects against the early stages of development of new breast cancers (ER positive and ER negative), then we would expect HT to protect against breast cancer in *BRCA1* mutation carriers (which are mostly ER negative).

We saw no association between the duration of HT use and the risk of breast cancer among *BRCA1* mutation carriers, and the association with past use was similar to that of current use. This observation is consistent with the hypothesis that transient exposure to HT is protective; ie, HT might induce the differentiation of precursor cancer cells and thereby prevent cancer later in life. It is of interest that both tamoxifen and oophorectomy are also effective in reducing the risk of postmenopausal breast cancer in *BRCA1* mutation carriers (4,16). It may be that estrogens and antiestrogens modify breast cancer risk at different stages of progression. For example, estrogen might act early in carcinogenesis, on stem cells or preneoplastic lesions, and tamoxifen and oophorectomy might act at a later stage, eg, in small established cancers.

Table 5. Risk of breast cancer by HT formulation*

Formulation	Control subjects, No.	Case patients, No.	OR (95% CI) Unadjusted	*P*	Multivariable	*P*
No HT	168	189	1 (referent)		1 (referent)	
Estrogen	40	28	0.53 (0.29 to 0.97)	.04	0.51 (0.27 to 0.98)	.04
Estrogen + progesterone	28	19	0.56 (0.30 to 1.04)	.07	0.66 (0.34 to 1.27)	.21

* Multivariable odds ratios adjusted for parity (0, 1, 2, or ≥3), oral contraceptive use (never vs ever), and country of residence. *P* values (two-sided) were calculated using conditional logistic regression. HT = hormone therapy; OR = odds ratio; CI = confidence interval.

Another possible reason for the inverse association we observed between HT and breast cancer risk in *BRCA1* mutation carriers is that estrogen increases expression of *BRCA1* (18). In cells that have not undergone loss of homozygosity (ie, that retain one normal *BRCA1* allele), this increase could lead to an increased cellular level of the wild-type protein, and thereby promote genetic stability.

There is one previous study of HT in *BRCA1* and *BRCA2* mutation carriers. Rebbeck et al. (9) examined the association between oophorectomy and breast cancer risk in a historical cohort study of 462 *BRCA1* and *BRCA2* mutation carriers. They found that the OR for breast cancer associated with oophorectomy was 0.40 (95% CI = 0.18 to 0.92) in the entire study group and 0.37 (95% CI = 0.14 to 0.96) in the subgroup of women with oophorectomy who used HT. However, in that study, use of HT was not evaluated independently of menopause because the sample size was small (there were only three women with breast cancer and HT exposure in the study by Rebbeck et al., compared with 47 in the current study).

Other areas of concern with regard to the secondary effects of HT in *BRCA1* mutation carriers include possibly elevated risks of endometrial and ovarian cancer. In the general population, estrogen alone is avoided in women with an intact uterus because of the established association between unopposed estrogen and endometrial cancer (17). In a recent study, we reported that the risk of endometrial cancer was increased in a cohort of carriers of *BRCA1* mutations, compared with noncarrier conrol subjects, but the increase was statistically significant only in those with past tamoxifen use (18). Of the six women with incident endometrial cancer observed in this earlier study, four women had a past history of tamoxifen use, but none had previously taken HT. A recent analysis of the Million Women Study (19) found an increased risk of 1.2 (95% CI = 1.1 to 1.3) for ovarian cancer in association with HT use. However, in a small study of HT in *BRCA1* and *BRCA2* mutation carriers (20), we did not see any increase in the risk of ovarian cancer in women with a past use of HT (OR = 0.93, 95% CI = 0.56 to 1.56).

The principal strength of our study is that we restricted our observations to postmenopausal women, that is, women who are candidates for HT. Case patients and control subjects were closely matched for age and age at menopause.

Our study also has limitations. One is the relatively small sample size. From a database containing more than 6000 patients, we studied 236 matched pairs of women with and without breast cancer. The average age at interview of the case patients and control subjects was 58 years. This subgroup represents a small proportion of the overall *BRCA1* mutation cohort; however, most women in the database could not contribute to the study, either because they had not yet reached menopause or because they had developed early-onset breast cancer. Women who had preventive mastectomy or who used tamoxifen were also excluded.

There is also the possibility of unmeasured confounders. By matching on age and type of menopause, we excluded the potential for bias that might arise if the age of menopause or type of menopause were correlated with the likelihood of receiving hormones. However, if other (currently unknown) factors correlate with the decision to take HT, these factors could potentially lead to a bias in the results.

Third, the validity of our results depends on the accuracy of the subjects' recall. The women in the study reported on the type of hormone preparation and the duration of use, but these values were not confirmed by review of medical records. Women who were unsure of the hormone formulation were excluded. We divided exposures by duration of HT but did not classify exposures according to the doses of the constituent hormones. It is also possible that case patients and control subjects differentially reported their history of hormone use, but recall bias would generate a spuriously elevated OR associated with the exposure, whereas we observed an inverse association.

Fourth, we studied prevalent cases; on average, 5.6 years had elapsed between the diagnosis of breast cancer and the completion of the questionnaire. If previous HT use was associated with a decreased survival of breast cancer following a diagnosis of breast cancer, then we may see few HT users among long-time breast cancer survivors, resulting in a spurious negative association.

In conclusion, these data are reassuring in suggesting that HT is probably not contraindicated in women with a *BRCA1* mutation. Although the data cannot yet be considered definitive, we observed a statistically significant reduction in the risk of breast cancer following HT use, in both the unadjusted and adjusted analyses. It is important that these findings be replicated. The observed associations were not different for women who used estrogen alone or estrogen plus progesterone. There was little difference in the observed ORs associated with less than 3 years and 3 or more years of exposure, and therefore it is not possible for us to recommend an optimum duration of use. We did not include patients with *BRCA2* mutations in this study because the sample size was small. It is important that these data be confirmed in other populations, including in women with *BRCA2* mutations. It is also important to evaluate the other risks and benefits associated with HT use in women at high risk for breast cancer.

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