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Hormone replacement therapy and the risk of ovarian cancer in *BRCA1* and *BRCA2* mutation carriers

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Abstract

Objective. Hormone replacement therapy (HRT) is commonly prescribed to alleviate the climacteric symptoms of menopause. Recent findings from the Women's Health Initiative has raised questions about the routine use of HRT due to the increased observed incidence of cardiovascular disease and of breast and ovarian cancers in the treatment arm of the trial. In the general population, the association between HRT use and risk of ovarian cancer has not yet been resolved. This association has not been evaluated in *BRCA1* or *BRCA2* mutation carriers who face very high lifetime risks of both breast and ovarian cancers.

Methods. We conducted a matched case-control study on 162 matched sets of women who carry a deleterious mutation in either the *BRCA1* or *BRCA2* gene. Women who had been diagnosed with ovarian cancer were matched to control subjects by mutation, year of birth, and age at menopause. Information on HRT use was derived from a questionnaire routinely administered to women who were found to be carriers of a mutation in either gene. Conditional logistic regression was used to estimate the association between HRT use and the risk of ovarian cancer, stratified by mutation status and type of HRT.

Results. Compared with those who had never used HRT, the odds ratio associated with ever use of HRT was 0.93 (95% CI = 0.56–1.56). There was no significant relationship with increasing duration of HRT use. There was a suggestion that progestin-based HRT regimens might protect against ovarian cancer (odds ratio = 0.57) but this association was not statistically significant (P = 0.20).

Conclusion. HRT use does not appear to adversely influence the risk of ovarian cancer in *BRCA* mutation carriers.

Keywords: *BRCA1*; *BRCA2*; Case-control study; Hormone replacement therapy; Ovarian cancer

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Introduction

Cancer of the ovary is the leading cause of death among women with gynecological malignancies. Approximately 12% of cases of invasive epithelial ovarian cancer are hereditary in nature and can be attributed to a *BRCA1* or *BRCA2* mutation [1]. The estimates for developing ovarian cancer among women who inherit a deleterious *BRCA1* or *BRCA2* mutation vary. Two recent studies have reported lifetime ovarian cancer risks of between 39–54% for *BRCA1* mutation carriers and 11–23% for *BRCA2* mutation carriers [2,3]. Mutations which occur within the central part of the *BRCA2* gene, commonly referred to as the ovarian cluster region (OCCR), confer a higher lifetime risk of ovarian cancer than mutations which occur in other regions of the gene [4,5]. Prophylactic bilateral salpingo-oophorectomy and tubal ligation are both protective [6]. Oral contraceptive use has also been shown to significantly reduce the risk of ovarian cancer among carriers [7–9] and in the general population [6], suggesting an important role of hormones on ovarian carcinogenesis.

Hormone replacement therapy (HRT) is commonly prescribed to help alleviate climacteric symptoms associated with menopause as well as for the prevention of chronic conditions such as osteoporosis [10]. Nonetheless, based on the results from the Women's Health Initiative (WHI), uncertainty exists surrounding the routine use of HRT. The WHI reported significant increases in the incidence of coronary heart disease and of breast cancer [11]; as well as a nonsignificant increase in the risk of invasive ovarian cancer in women assigned to the estrogen plus progestin arm of the trial compared with those receiving placebo (hazard ratio = 1.6; 95% confidence interval 0.77–3.24) [12]. Data regarding HRT use and the risk of ovarian cancer in the general population are contradictory, with various studies reporting an increased risk, particularly among long-term users, and other studies reporting a decreased risk, or no association (reviewed in [6]). Some authors suggest that risk may also vary with the type of HRT as well as with the duration of use and mode of administration [13]. This association has not been evaluated among *BRCA* mutation carriers and it is of interest to study this subset of women who face high lifetime risks of ovarian cancer. We conducted the present study to examine whether the use of HRT influences the risk of ovarian cancer in women who carry a mutation in the *BRCA1* or *BRCA2* gene.

Materials and methods

Study population and data collection

Eligible study subjects included living women who were identified from 55 participating centers in eight countries. These women were participants in ongoing clinical research protocols (or a research protocol for the University of Utah participants) at the host institutions. All study subjects received counseling (with the exception of those from the University of Utah), provided written informed consent for genetic testing and completed a questionnaire that asked about their medical and reproductive histories, and selected lifestyle factors including past and current HRT use. The subjects were asked if they have ever taken HRT, what year they began using HRT, at what year they stopped using HRT, the total duration of HRT use, and if they currently use HRT. Information about the type of HRT was also requested. Questionnaires were administered at the individual centers at the time of a clinic appointment or at their home at a later date. Additional variables of interest included information on demography and ethnic group.

The institutional review boards of the host institutions approved the study. 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 relative, genetic testing was offered to other at-risk women in the family. Mutation detection was performed using a variety of techniques, but the nucleotide sequence of all mutations was confirmed by direct sequencing of DNA. A woman was eligible for the current study when the molecular analysis established that she was a carrier of a deleterious mutation in the *BRCA1* or *BRCA2* gene. Most (>95%) of the mutations identified in the study subjects were either nonsense mutations or small insertion/deletion mutations resulting in a reading frame-shift.

Information on cancer history was available for a total of 6180 women who carried a *BRCA1* or *BRCA2* mutation. For this study, we only included women who reached natural menopause (i.e. who had intact ovaries). 4812 women had not reached menopause, or had surgical menopause, and were therefore not eligible. We also excluded women for several other reasons, including a diagnosis of ovarian cancer prior to menopause (300 women), and a diagnosis of breast or any other cancer prior to ovarian cancer because a cancer diagnosis is likely to influence their choice to use HRT (89 women). Other reasons for excluding women included missing information regarding HRT use (41 women) or age at menopause (37 women). Potential subjects were also excluded if tamoxifen or HRT was used prior to menopause (62 women). After exclusions, there were 838 eligible women, including 171 women with ovarian cancer (potential case subjects) and 667 women without ovarian cancer (potential control subjects).

Potential case subjects had a history of invasive ovarian, fallopian tube, or peritoneal cancer, as well as cancer of the omentum. Control subjects were women who never had ovarian cancer and who were carriers of a mutation in the *BRCA1* or *BRCA2* gene. One or more

controls were selected for each case subject matched according to mutation in the same gene (*BRCA1* or *BRCA2*), year of birth (within 3 years), and age at menopause (within 3 years). In addition, the diagnosis of any other cancer or bilateral oophorectomy of the control had to have occurred after the year of breast cancer diagnosis of the matched case subject. HRT use of the control was censored at the age of ovarian cancer diagnosis of the matched case. A total of 162 matched sets were generated, including 117 pairs with *BRCA1* mutations and 45 pairs with *BRCA2* mutations. On average, there were approximately 2.3 controls per case (range 1–7 controls per case). Among the cases, there were 155 women with a diagnosis of a primary ovarian cancer, four women with a primary fallopian cancer, two women with primary peritoneal cancer, and one woman with both ovarian and fallopian cancers.

Data analysis

A matched case-control analysis was performed. The mean duration of HRT use in the case and control subjects was compared by using the Student's *t* test. This test statistic was also used for all other continuous variables. The chi-square test was used to test for differences in categorical variables. The univariate odds ratios (ORs) and 95% confidence intervals (CIs) for breast cancer associated with HRT use and the type of HRT were estimated using conditional logistic regression for matched sets with a variable number of cases and controls. HRT preparations were divided into those containing estrogen, progesterone, or both, and estimates of the odds ratio were made for each exposure subgroup. Estrogen and progestin were considered separately in the model by including individual regression terms for estrogen and progestin. A multivariate analysis was carried out to control for the potential confounding effects of oral contraceptive (OC) use, parity, and country of residence. OC use was coded as ever or never user, and parity was coded as zero, one, two, and three or more births. Data analyses were also performed for *BRCA1* and *BRCA2* mutation carriers separately. All statistical tests were two-sided. All analyses were performed using the SAS statistical package, version 8.1 (SAS Institute, Cary NC).

Results

We identified a total of 162 matched sets for the case-control analysis. The case and control subjects were similar with respect to date of birth, age at menopause, smoking status, and parity (Table 1). Compared with the control subjects, a significantly lower proportion of case subjects had ever used an oral contraceptive (34.4% versus 49.1% for case and control subjects, respectively: $P = 0.002$).

Table 1
Comparison of case and control subjects with *BRCA1* and *BRCA2* mutations

Variable	Case subjects $n = 162$	Control subjects $n = 375$	P[a]
Date of birth, mean year (SD)[b]	1936.8	1937.3	0.59
Age at interview, mean (range)	62.7 (48–85)	61.2 (48–86)	0.51
Age at ovarian cancer diagnosis, mean (range)			
BRCA1	57.2 (42–83)		
BRCA2	61.5 (47–77)		
Age at menopause, mean (range)			
BRCA1	49.1 (37–56)	49.4 (39–58)	0.48
BRCA2	49.7 (43–55)	49.8 (43–56)	0.83
Mutation, *n* (%)			
BRCA1	117 (72.2)	256 (68.3)	
BRCA2	45 (27.8)	119 (31.7)	
HRT use			
Never, *n* (%)	117 (72.2)	290 (77.9)	
Ever, *n* (%)	45 (27.8)	83 (22.1)	0.33
Mean year for user (SD)	3.6 (2.9)	5.5 (4.5)	0.006
Oral contraceptive use, *n* (%)			
Never	103 (65.6)	186 (50.8)	
Ever	54 (34.4)	180 (49.1)	0.002
Smoke history, *n* (%)			
Never	94 (58.8)	198 (56.1)	
Ever	66 (41.2)	155 (43.9)	0.57
Parity[c], mean (SD)	2.6 (1.7)	2.7 (1.8)	0.34
Country of residence[d], *n* (%)			
USA	60 (37.0)	113 (30.1)	
Canada	51 (31.5)	103 (27.5)	
Poland	21 (13.0)	57 (15.2)	
Europe, other[e]	17 (10.5)	67 (17.9)	
Israel	13 (8.0)	35 (9.3)	

[a] All *P* values are univariate and were derived using the Student's *t* test for continuous variables and the chi-square test for categorical variables.
[b] SD = standard deviation.
[c] Parity includes live born and still born, and was included only in analysis if birth was one calendar year before the age of diagnosis of the matched case.
[d] Country of residence at time of testing.
[e] Includes women from the Netherlands ($n = 29$ sets), Italy ($n = 17$ sets), Norway ($n = 32$ sets), Sweden ($n = 5$ sets), and the United Kingdom ($n = 1$ set).

We examined the relationship between HRT use and the risk of ovarian cancer in women with a *BRCA1* or *BRCA2* mutation (Table 2). Compared with those who had never used HRT, the OR associated with ever use of HRT was 0.93 (95% CI = 0.56–1.56). Following stratification by mutation status, HRT use was not associated with the risk of *BRCA1*- or *BRCA2*-associated ovarian cancer (Table 2). Although there was no difference in the proportion of women who ever used HRT, the average duration of HRT use was lower for the case subjects versus the control subjects (5.4 years versus 7.6 years; $P = 0.05$). There was no significant dose–response relationship associated with increasing duration of HRT use (Table 2). Including parity and OC use in the multivariate analysis had minimal effects on the final ORs.

The type of HRT used was also studied (Table 3). Although not significant, women who ever used either an estrogen (either an estrogen or estrogen + progestin-based

Table 2
Association between ovarian cancer risk and hormone replacement therapy use in *BRCA* mutation carriers, all and stratified by mutation

Group	Controls, *n* (%)	Cases, *n* (%)	Crude odds ratio (95% CI)	*P*	Adjusted odds ratio (95% CI)[a]	*P*
All						
HRT use						
Never	292 (77.9)	120 (74.1)	1.00 (referent)		1.00 (referent)	
Ever	83 (22.1)	42 (25.9)	1.11 (0.70–1.77)	0.65	0.93 (0.56–1.56)	0.79
P trend[b]			0.94	0.08	0.92	0.05
BRCA1 mutation carriers						
HRT use						
Never	205 (80.1)	87 (74.4)	1.00 (referent)		1.00 (referent)	
Ever	51 (19.9)	30 (25.6)	1.13 (0.66–1.92)	0.67	0.92 (0.50–1.70)	0.80
P trend			0.96	0.96	0.93	0.14
BRCA2 mutation carriers						
HRT use						
Never	87 (73.1)	33 (73.3)	1.00 (referent)		1.00 (referent)	
Ever	32 (26.9)	12 (26.7)	1.08 (0.44–2.67)	0.87	0.89 (0.29–2.39)	0.74
P trend			0.89	0.11	0.89	0.22

[a] All ORs were derived using multivariate conditional logistic regression and were adjusted for parity (0, 1, 2, and ≥3), OC use (never/ever) and country of residence.
[b] *P* trend is based on increments of one year of HRT use.

HRT) had a modestly increased risk of ovarian cancer compared with never users of HRT (OR = 1.50; 95% CI = 0.73–3.11). In contrast, ever use of progestin (progestin or estrogen + progestin) appeared to decrease the risk of ovarian cancer (OR = 0.57; 95% CI = 0.24–1.35). The magnitudes of these associations were lessened after adjusting for covariates.

Discussion

The results of this study show that HRT use has little effect on the risk of ovarian cancer in women who carry a deleterious *BRCA1* or *BRCA2* mutation. Adjustment for parity and oral contraceptive use did not substantially influence the association. These results are in accordance with other studies that have reported no association between HRT use and the development of ovarian cancer in the general population [14–19].

Results from other epidemiological studies are inconclusive and suggest that the magnitude and direction of the association between HRT use and ovarian cancer may be modified by the duration and type of HRT used (reviewed in [6]). The positive associations that have been documented have generally been found for users of unopposed estrogen replacement therapy versus users of combined estrogen–progestin replacement therapy (reviewed in [13]). In our study, stratifying by the type of HRT used showed a possible protective role of progestin-based formulations but these results were not significant. The most commonly prescribed formulation of HRT for women undergoing natural menopause (with an intact uterus) includes a combination of estrogen plus progestin therapy to reduce the risk of uterine endometrial cancer [20–22].

Various hypotheses that may explain the development of ovarian cancer have been proposed and include the 'incessant ovulation' hypothesis in which the increased rate of cell division associated with ovulation, as well as exposure to high levels of estrogen may contribute to the development of ovarian cancer. Other hypotheses include stimulation of the ovarian epithelium through exposure to elevated levels of gonadotropins, retrograde transportation of carcinogens, impaired apoptosis, and an imbalance of sex hormones (reviewed in [6]). The role of HRT use in the

Table 3
Association between ovarian cancer risk and hormone replacement therapy use in *BRCA* mutation carriers, stratified by type of HRT

Type of HRT	Controls, *n*	Cases, *n*	Crude odds ratio (95% CI)	*P*	Adjusted odds ratio (95% CI)[a]	*P*
Never	292	120	1.00 (referent)		1.00 (referent)	
Estrogen containing[b]	65	31	1.50 (0.73–3.11)	0.27	1.02 (0.47–2.22)	0.96
Progestin containing[c]	48	19	0.57 (0.24–1.35)	0.20	0.80 (0.32–2.00)	0.63
Unknown	15	9	1.33 (0.52–3.40)	0.55	0.97 (0.36–2.61)	0.95

[a] All ORs were derived using multivariate conditional logistic regression and were adjusted for parity (0, 1, 2, and ≥3), OC use (never/ever) and country of residence.
[b] Includes women who ever used estrogen (either estrogen or estrogen + progestin-based HRT).
[c] Includes women who ever used progestin (either progestin or estrogen + progestin-based HRT).

etiology of ovarian cancer remains unclear. The mitogenic and mutagenic effects of estrogen may promote carcinogenesis, whereas the pro-apoptotic actions of progesterone may confer protection (reviewed in [23]). Expression of both estrogen and progesterone receptors has been documented in the normal ovarian surface epithelium as well as in sporadic ovarian cancers [24,25]. To date, there have been no studies looking at the receptor patterns of familial ovarian cancers.

One drawback of our study is the use of self-reported exposure data which may have introduced measurement error. Although HRT use reported by the women in our study was not validated against clinical records, others have shown a high level of concordance between HRT use obtained through a questionnaire and information obtained from prescription forms [26]. The potential of recall bias is minimal since there was no a priori reason for the women to suspect such risk factors in the etiology of their disease. Only women who underwent natural menopause were included in this study. Following surgical menopause (oophorectomy), *BRCA1* carriers are at a reduced risk of ovarian cancer. This is of particular relevance in our target population since prophylactic oophorectomy is a common recommendation to *BRCA*-carriers after childbearing years to minimize risks against both breast and ovarian cancer [9,27]. HRT is commonly prescribed to alleviate early menopausal symptoms; however, the results of the present study are relevant to *BRCA* mutation carrier women who choose to undergo natural menopause.

Our study is the first to address the role of HRT use specifically on the risk of hereditary ovarian cancer. The primary strength of our study is the relatively large sample of known *BRCA* mutation carriers restricted to women who underwent natural menopause and who had their ovaries intact. Our matching strategy and exclusion criteria resulted in case and control groups that were similar in most respects. We believe that our study participants are representative of women who have had *BRCA* mutations identified during the course of genetic counseling. Our study was based on known mutation carriers and included patients from numerous participating centers and of different ethnic backgrounds.

There have been no published studies to date investigating a role of HRT in the etiology of breast cancer in *BRCA1*- or *BRCA2*-mutation carriers. These studies are underway. Although we found that HRT use did not increase the risk of ovarian cancer, there is a need to consider other risks and benefits, including those of cardiovascular disease and breast cancer, in order to provide informed choices about HRT use to members of this high-risk population.

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