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Risk Factors for Endometrial Cancer among Women with a *BRCA1* or *BRCA2* Mutation: A Case Control Study

Yakir Segev[1,2], **Barry Rosen**[2], **Jan Lubinski**[3], **Jacek Gronwald**[3], **Henry T. Lynch**[4], **Pal Moller**[5], **Charmaine Kim-Sing**[6], **Parviz Ghadirian**[7], **Beth Karlan**[8], **Charis Eng**[9], **Dawna Gilchrist**[10], **Susan L. Neuhausen**[11], **Andrea Eisen**[12], **Eitan Friedman**[13], **David Euhus**[14], **Sun Ping**[1], **Steven A. Narod**[1,*], and **the Hereditary Breast Cancer Study Group**

[1]Women's College Research Institute, 790 Bay Street, Toronto, ON, M5G 1N8, Canada [2]Department of Obstetrics and Gynecology, University of Toronto and Gynecologic Oncology, Princess Margaret Hospital, Toronto, ON, M5G 2M9, Canada [3]International Hereditary Cancer Center, Pomeranian Medical University, Szczecin, Poland [4]Department of Preventive Medicine and Public Health, Creighton University School of Medicine, Omaha, NE, 68178 USA [5]Inherited Cancer Research Group, The Norwegian Radium Hospital, Department for Medical Genetics, University Hospital, Oslo, Norway [6]BC Cancer Agency, BC, V5Z 1L3, Canada [7]Epidemiology Research Unit, Research Centre of the University of Montreal Hospital Centre (CRCHUM), Montreal, QC, Canada [8]Department of Obstetrics and Gynecology, Cedars-Sinai Medical Center, Beverly Hills, CA, USA [9]Genomic Medicine Institute, Cleveland Clinic, Cleveland, OH, USA [10]Department of Medical Genetics, University of Alberta, Edmonton, Alberta, Canada [11]Department of Population Sciences, Beckman Research Institute, City of Hope, Duarte, CA, 91010, USA [12]Sunnybrook Regional Health Sciences Center, Toronto, ON, Canada [13]Susanne Levy Gertner Oncogenetics Unit, Sheba Medical Center, Tel-Hashomer, Israel [14]Department of Surgery, John Hopkins University, Baltimore, MD, 21218, USA

Abstract

Purpose—*BRCA* mutation carriers may use tamoxifen for breast cancer prevention or treatment. Hormone replacement therapy is often prescribed after surgical menopause and oral contraceptives are recommended for ovarian cancer prevention. The objective of this study was to assess the impact of these medications and other risk factors on endometrial cancer risk in *BRCA* carriers.

Methods—Women with a *BRCA1* or *BRCA2* mutation were identified from a registry of mutation carriers. Cases were 83 women who had a diagnosis of endometrial cancer. Controls

[*]Corresponding Author: Steven A. Narod, Women's College Research Institute, Familial Breast Cancer Research, 790 Bay Street, 7th floor, Toronto, ON, Canada M5G 1N8, steven.narod@wchospital.ca, Phone: +1 416 351 3765, Fax: +1 416 351 3767.

Other members of the Hereditary Breast Cancer Clinical Study Group: Ophira Ginsburg, André Robidoux, Lovise Maehle, Kevin Sweet, Leigha Senter, Olufunmilayo Olopade, Peter Ainsworth, Fergus Couch, Claudine Isaacs, Jeffrey N. Weitzel, Nadine Tung, Mary B. Daly, Judy E. Garber, Dana Zakalik, Carey A. Cullinane, Dominique Stoppa-Lyonnet, Howard Saal, Wendy Meschino, Wendy McKinnon, Marie Wood, Taya Fallen, Raluca Kurz, Siranoush Manoukian, Susan Armel, Rochelle Demsky, Jeanna McCuaig, Edmond Lemire, Jane McLennan, Seema Panchal, Louise Bordeleau, Albert E. Chudley, Susan T. Vadaparampil, Tuya Pal, Daniel Rayson, Susan Friedman (on behalf of FORCE), Cezary Cybulski, Tomasz Byrski, Tomasz Huzarski,

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were 1027 matched women who did not develop endometrial cancer and who had an intact uterus. All women completed a baseline questionnaire, which included questions about ages at menarche and menopause, oral contraceptive use, hormone replacement therapy use, hysterectomy, oophorectomy, breast cancer history and tamoxifen use. We estimated the odds ratio associated with each risk factor in a multivariate analysis.

Results—No differences were found between cases and controls in terms of age at menarche, BMI, smoking, or oral contraceptive use. In a multivariate analysis, for women taking estrogen-only hormone replacement therapy, the odds ratio was 0.23 (95% CI 0.03–1.78, p = 0.16), and for women taking progesterone-only hormone replacement therapy the odds ratio was 6.91 (95% CI 0.99–98.1, p = 0.05). The adjusted odds ratio for endometrial cancer associated with a history of tamoxifen use was 3.50 (95% CI 1.51 to 8.10; p = 0.003).

Conclusions—The observed increased risk of associated with progesterone-only therapy merits further study.

Keywords

Endometrial cancer; tamoxifen; BRCA1; BRCA2

INTRODUCTION

Endometrial cancer is the most common malignancy of the female genital tract in Western countries, where it accounts for approximately 6% of all newly-diagnosed cancers in women [1]. Several risk factors have been implicated, including hormone replacement therapy [2], exposure to tamoxifen [3], excess body weight [4], lack of physical activity [5], early menarche [6], infertility and anovulation, low parity, late menopause [7], and a family history of endometrial cancer [8]. Carriers of mutations in the BRCA genes face elevated risks of both breast and ovarian cancer. Some studies suggest that BRCA1 mutation carriers are at elevated risk for endometrial carcinoma, mainly of the uterine serous histologic subtype [9–11]. In a recent study [12], we followed 4456 women with a BRCA1 or a BRCA2 mutation for incident cases of endometrial cancer. The Standard Incidence Ratios (SIR) for BRCA1 carriers was 1.91 (95% CI: 1.06–3.19, p = 0.03) and for BRCA2 carriers was 1.75 (95% CI: 0.55–4.23, p = 0.2). The risk was elevated for women who took tamoxifen, but the risk estimates were based on only 17 incident cases of endometrial cancer.

BRCA carriers often experience early surgical or natural menopause and many are prescribed hormone replacement therapy after surgery. They may also take tamoxifen for prevention, or as adjuvant treatment for breast cancer. It is important to know if the side effects of these medications include endometrial cancer in genetically-predisposed women. In the general population, tamoxifen has agonist activity on the endometrium and increases the risk for endometrial hyperplasia and subsequently of endometrial cancer [13,14]. *BRCA* mutation carriers may take oral contraceptives for fertility control and/or to decrease their risk for ovarian cancer [15]. In the general population, oral contraceptives have a protective effect on endometrial cancer with a 50% decrease in risk for long term use [16]. We sought

to evaluate the effects of various hormonal therapies on the risk of endometrial cancer in women who carry a mutation in the *BRCA1* or *BRCA.*

MATERIALS AND METHODS

Patients and procedures

Women with a *BRCA1* or *BRCA2* mutation were identified through a registry of mutation carriers at the Women's College Research Institute. Data were collected from women with a known pathogenic *BRCA1* or *BRCA2* mutation at 50 different centres in eleven countries in North America, Europe, and Israel. The ethics committees/human subjects review boards at all participating centres approved the study protocol. Informed consent was obtained from all women prior to genetic testing. When a *BRCA1* or *BRCA2* mutation was identified in a proband or her relative, genetic testing was offered to other at-risk individuals in the family. Mutations were identified using a range of screening techniques, but all abnormal nucleotide sequences were confirmed by direct sequencing of DNA in the host laboratory or in a commercial laboratory.

All women completed a risk factor questionnaire at study entry. The questionnaire collected information on key variables, including personal histories of cancer and relevant cancer risk factors, including ages at menarche and menopause, oral contraceptive use, hormone replacement therapy (HRT) use, hysterectomy, oophorectomy, breast cancer and tamoxifen use. At some centres, the questionnaires were completed by telephone interview. A woman was eligible for the study if the molecular analysis established that she was a carrier of a deleterious mutation in either the *BRCA1* or *BRCA2* gene.

A total of 14,834 women were identified as potentially eligible for the study. We excluded 169 subjects for whom key data elements were missing. We excluded three women who had a diagnosis of ovarian cancer prior to endometrial cancer. We excluded 41 women who had a mutation in both genes. The remaining 14,621 women were eligible to be subjects of the present study. We conducted a matched case-control study with a variable number of controls per case. A case was defined as a woman who had a diagnosis of endometrial cancer. A control was defined as a woman who had not had endometrial cancer. A control was eligible to be matched to a given case if she had an intact uterus at the date of diagnosis of the matched case. For each case, one or more controls were selected; cases and controls were matched on date of birth (± two years), past history of breast cancer (if yes ± two years in age of diagnosis), country of residence and *BRCA* mutation status (*BRCA1* or *BRCA2*). Through this process, we generated 80 matched sets, consisting of 83 cases (62 *BRCA1* and 21 *BRCA2*), and 1027 controls (951 *BRCA1* and 76 *BRCA2*) (mean of 9 controls per case).

Analysis

Cases and controls were compared for a number of variables: parity, age at menarche, tamoxifen use (for treatment or prevention), duration of tamoxifen use, menopausal status, oral contraceptive use, hormone replacement treatment use, smoking, prior oophorectomy and BMI (calculated as weight divided by the square of height). Student's t test was used to test for statistical significance for continuous variables (comparing the mean of means) and

the Chi-squared test was used for categorical variables. To estimate the odds ratio associated with each risk factor, a matched analysis was done using conditional logistic regression with a variable ratio of controls to cases. Initially, a univariable analysis was conducted. To adjust for potential confounding, a multivariable analysis was done. The multivariable adjusted odds ratios and 95% confident intervals were estimated using SAS (version 9.1.3) and $p < 0.05$ was considered to be statistically significant.

RESULTS

We identified 80 cases and 956 controls. Cases and controls were well-balanced with respect to year of birth, age at questionnaire completion and country of residence (Table 1). Sixty-two (74.7%) cases were *BRCA1* carriers compared to 951 (93.9%) of controls (the difference was taken into account by our matched analysis). No differences were found between the cases and controls in terms of age of menarche or smoking history. We compared the BMI of cases and controls at three ages: age 18, 30 and 40 years. No differences in BMI between the groups were noted at any age. The mean age at menopause was 45.4 for controls and was 45.5 for cases ($p = 0.97$). Mean parity among cases was 2.00 and among controls was 2.10 among controls ($p = 0.50$). Fifteen (19.5%) of the cases reported having had a prior oophorectomy, compared to 285 (27.9%) of the controls ($p = 0.10$). Oral contraceptives were taken by 43 cases (54.4%) and 403 controls (43.7%) (Table 1).

We performed univariable and multivariable conditional logistic regression analyses to assess the association between each risk factor and the risk of endometrial cancer. In the multivariable analysis (adjusting for age, parity, tamoxifen use, hormone replacement therapy use, prior oophorectomy, menopause and smoking), the odds ratio for endometrial cancer associated with oral contraceptive use was 1.49 (95% CI 0.74–2.99, $p = 0.26$). In the multivariate analysis, the odds ratio for menopause was 1.42 (95% CI 0.63–3.21, $p = 0.39$), and the odds ratio for prior oophorectomy was 0.51 (95% CI 0.27 –0.97; $p = 0.04$).

Thirteen cases (16.9%) and 157 controls (15.9%) had taken hormone replacement therapy (Table 1). In the multivariable analysis, the adjusted odds ratio for endometrial cancer associated with any hormone replacement treatment was 0.73 (95% CI 0.33–1.63, $p = 0.44$). Among cases, two took estrogen replacement therapy, eight took a combination of estrogen and progesterone and two took progesterone-only replacement therapy (Table 1). Two women developed endometrial cancer after taking estrogen only; the first took Premarin from age 47 to 49 and developed endometrial cancer at age 66, the second took Premarin from age 36 to 45 and developed endometrial cancer at age 45 while using the drug. Two women developed endometrial cancer after taking progesterone only; the first took Provera for one year at age 51 and developed endometrial cancer at age 59, the dates for the other patients were not recorded.

In a multivariate analysis, for women taking estrogen-only hormone replacement therapy, the odds ratio was 0.23 (95% CI 0.03–1.78, $p = 0.16$), and for women taking progesterone-only hormone replacement therapy the odds ratio was 6.91 (95% CI 0.99–48.1, $p = 0.05$).

Among all study subjects, 20.5% of all cases reported ever having used tamoxifen, compared to 7.4% of controls (OR = 3.50; 95% CI, 1.51–8.10 p = 0.003). The mean duration of tamoxifen use among all cases was 1.14 years compared to 0.41 years among controls (p = 0.02) (Table 1). Tamoxifen was used for treatment of breast cancer by 16 (34.8%) cases and by 65 (16.5%) controls. In the breast cancer subgroup, in the univariable analysis, the odds ratio for endometrial cancer given tamoxifen treatment was 5.75 (95% CI 2.25 to 14.7, p = 0.0003) (Table 2). The adjusted odds ratio for endometrial cancer associated with tamoxifen treatment was 6.21 (95% CI 2.21 – 17.5 p = 0.0005). The hazard ratios by specific genetic subgroup are published in Tables 3 and 4.

DISCUSSION

Women with a *BRCA1* or *BRCA2* mutation represent a unique population at high risk for breast and ovarian cancer. Many will use tamoxifen, either for the prevention or treatment of breast cancer. Tamoxifen is a competitive inhibitor of estrogen binding to estrogen receptors, and has agonist and antagonist activities, depending on the target tissue [13, 14]. Tamoxifen has an agonist action on the endometrium, where it induces endometrial hyperplasia and increases the risk of subsequent endometrial cancer [17, 18]. Fisher and colleagues estimated the adjusted relative risk for endometrial cancer among breast cancer patients above the age of 50 to be 5.33 associated with tamoxifen use, compared to no use [19]. The relative risk was 1.42 for patients below 50 years old [19].

Recently, we estimated the annual risk of endometrial cancer in a cohort study of 4456 *BRCA1* and *BRCA2* mutation carrier women, and found the risk to be higher in *BRCA1* mutation carriers than in the general population [12]. The excess risk was due in large part to the use of tamoxifen; the SIR for endometrial cancer was 4.14 for women who had taken tamoxifen and was 1.67 for women who had not taken tamoxifen. In the current case-control study, we extend the number of cases of endometrial cancer from 17 to 83 and include 1027 matched controls. Using this case-control design, we were able to confirm this association of tamoxifen and endometrial cancer in a second series of non-overlapping cases.

Hormone replacement therapy is offered to *BRCA* carriers who have no history of breast cancer. Many patients undergo prophylactic bilateral oophorectomy to decrease their risk for ovarian and breast cancer; in young women this increases the risk for menopausal symptoms. Hormone replacement therapy is used to alleviate those symptoms. In a previous study, we found that hormone replacement therapy does not increase the risk for breast cancer among BRCA carriers [20]. In the present study, we found no overall association between hormone replacement and endometrial cancer (OR = 0.73 (95% CI, 0.33–1.63; p = 0.44). This is in contrast to studies in the general population; several case-control studies and prospective studies in non-carriers have shown an increased incidence of endometrial carcinoma among women taking unopposed estrogen (i.e., without progesterone) with relative risks ranging from 1.1 to 15 [21,22]. The risk of endometrial cancer is related to both the estrogen dose and the duration of hormone replacement and can be reduced by the concomitant administration of a progestin [22, 23]. In the current study, we observed a borderline significant increased risk of endometrial cancer among *BRCA* carriers who used

a progesterone-only formulation and a decreased risk among carriers who used an estrogen-only formulation. This was based on a small number of exposed subjects.

A systematic review of 19 observational studies found that ever use of oral contraceptives decreased the risk of endometrial cancer by approximately 50 percent in the general population and that the protective effect persisted for 10 to 20 years after cessation of use [16]. The benefit of oral contraceptives is believed to be due to the progestin component, which suppresses endometrial proliferation. We did not find a protective effect from oral contraceptives (adjusted odds ratio 1.49; 95% CI, 0.74–2.99 p = 0.26). We do not have information regarding the specific regimen of oral contraceptive use.

In previous reports, the risk of endometrial carcinoma was inversely related to parity. McPherson et al. analyzed data from a cohort of 24,848 postmenopausal women. During follow-up, 167 incident endometrial cancer cases were documented [24]. The mean gravidity of cases was lower than that of non-cases (2.6 vs. 3.5, $p < 0.0001$) [24]. Løchen et al. reported that women with 8 to 11 children had a relative risk of 0.35 for death from endometrial cancer (95% CI, 0.14–0.85) compared to nulliparous women [25]. In that study, for a first birth at age greater than 34 years, versus less than 19 years, the relative risk was 0.53 (95% CI 0.34–0.83) [25]. In the current study, parity was associated with a modest, but non-significant decrease in the risk for endometrial cancer on a multivariate analysis, OR = 0.92 (95% CI, 0.75–1.13; p = 0.42).

Late menopause is a risk factor for endometrial cancer, believed to be due to prolonged estrogen stimulation during the reproductive years [24]. In our study, the adjusted odds ratio for endometrial cancer associated with menopause was 1.42 (95% CI, 0.63–3.21; p = 0.39).

Cigarette smoking has been associated with a decreased risk of developing endometrial carcinoma in postmenopausal women. In a meta-analysis of 34 prospective and case-control studies, the risk was significantly reduced for postmenopausal endometrial cancer (RR 0.71, 95% CI 0.65–0.78), but not for premenopausal endometrial cancer (RR 1.06, 95% CI 0.88–1.28) [26]. In our study, among *BRCA* carriers who were past smokers, the odds ratio for endometrial cancer was 1.08 (95% CI, 0.63–1.84; p = 0.26) (pre-and post-menopausal cases combined).

Taken together, these observations suggest that, with the exception of tamoxifen, the risk factors for endometrial cancer are different in the general population and in BRCA1 carriers (the number of BRCA2 carriers was too small to support any conclusions in this subgroup). In both BRCA carriers and in non-carriers, tamoxifen promotes endometrial cancer. However, in the general population, estrogen is an endometrial carcinogen and its effect is mitigated by progesterone. Our data (although based on only two exposed cases) suggests the opposite might be true in BRCA1 carriers. We found no increase in endometrial cancer risk in conditions associated with increased estrogen exposure (obesity, unopposed estrogen) and no protective effect in conditions associated with hypo-estrogenism (smoking, menopause). In contrast, progesterone exposure did not appear to protect against endometrial cancer BRCA1 carriers, either in the form or hormonal replacement therapy or as an oral contraceptive. Although the number of exposed cases was very small,

progesterone-only therapy was associated with an increase in endometrial cancer risk in BRCA1 carriers in both the unadjusted (OR = 7.49; 95% CI 1.2 to 47; p = 0.03) and in the adjusted analysis (OR = 16.5 (95% CI 2.02 to 134; p = 0.009). Recently, Widschwendter and colleagues reported that women with a BRCA1 mutation had higher than expected serum progesterone levels than non-carriers [27]. In that study, luteal phase levels of progesterone were 121% higher in carriers than in non-carriers (p< 0.0001).

Rajan et al. reported that Brca1 and Brca2 mRNA expression are differentially regulated by sex hormones [28]. Perhaps the signaling pathways which link progesterone and/or estrogen exposure to endometrial cell proliferation are disrupted in the absence of the full complement of the BRCA1 protein. To our knowledge, no studies have been done on the expression progesterone receptor (PR) in the endometrium of BRCA1 carriers and controls, but King et al have shown that PR expression is greater in normal breast tissue of BRCA1 carriers than in non-carrier controls [29]. BRCA1 inhibits PR signaling in breast cancer cells [30] and Rosen and his colleagues propose that breast cells deficient in BRCA1 may be hyper-sensitive to the effect of endogenous progesterone [31]. It will be of interest to extend these observations to studies of the endometrium as well.

The main limitation of our study is the small number of endometrial cancer cases. We identified 83 cases from a database of over 13,000 carriers and only 13 of the cases had exposure to HRT. We do not have information on the specific histologic subtype of endometrial cancer cases and risk factors may differ between type 1 and type 2 endometrial cancers. However, in a recent study, Setiawan et al found that the risk factors for the two subgroup of endometrial cancer were similar [32]. Our patient sample is also unusual in that the average age of diagnosis of endometrial cancer was 51.6 years and the oldest case was diagnosed at age 67. This is because of the average age of members of the cohort at study entry was 56 years and the risk of endometrial cancer does not peak until much later. It will be important to revisit the cohort at a later date and to conduct a second analysis when there are more cases of endometrial cancer diagnosed among women in their sixties and seventies.

In conclusion, we found that the risk for endometrial cancer among BRCA1 and BRCA2 carriers was increased approximately three-fold after treatment with tamoxifen. We estimated that the attributable risk for endometrial cancer was 2% associated with a five year course of tamoxifen [12] and we recommend that BRCA1 carriers who take tamoxifen might benefit from a hysterectomy in addition to oophorectomy. The use of raloxifene for cancer prevention in the general population has been proposed to reduce the risk of endometrial cancer in post-menopausal women [33] but no studies of raloxifene in BRCA carriers have been published. In this study, the use of estrogen-based hormone replacement therapy did not increase the risk for endometrial cancer. Paradoxically, we observed an increase in risk associated with progesterone-only hormone replacement therapy and oral contraceptives did not protect against endometrial cancer, but these data are preliminary. These data suggest that hormonal risk factors for endometrial cancer may not apply equally for carriers of BRCA1 or BRCA2 mutations, but further studies are necessary.

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Table 1

Comparison of Endometrial Cancer Cases and Controls

Variables	Cases N = 83	Controls 83 sets (N = 1027)	P-value
Date of birth	1949.2 (1925–78)	1948.9(1926–76)	0.85
Age at baseline	55.5 (30–76)	56.1 (29–78)	0.65
Age at diagnosis	51.6 (23–67)	NA	
Parity			
mean	2.00 (0–6)	2.10 (0–7)	0.50
0	12 (14.5%)	126 (12.4%)	
1–4	70 (84.3%)	845 (82.9%)	
5	1 (1.2%)	48 (4.7%)	0.30
Age at first born	24.9 (18–39)	24.5 (15–43)	0.57
Age at menarche	13.1 (10–19)	13.1 (9–17)	0.73
Mutation			
BRCA1	62 (74.7%)	951 (92.6%)	
BRCA2	21(25.3%)	76 (7.4%)	Matched
Breast cancer			
No	37 (44.6%)	633 (61.6%)	Matched
Yes	46 (55.4%)	394 (38.4%)	
Age at diagnosis	46.9 (27–76)	47.0 (24–74)	0.94
Tamoxifen for prevention			
No	81 (98.0%)	1014 (98.7%)	
Yes	2 (2.4%)	13 (1.3%)	0.39
Mean used yrs (all subjects)	0.09 (0–4.8)	0.03 (0–10.0)	0.38
Mean used yrs (users only)	3.94	2.62 (0.1–10)	0.56
Tamoxifen for treatment			
No	30 (65.2%)	329 (83.5%)	
Yes	16 (34.8%)	65 (16.5%)	0.003
Mean use yrs (all subjects)	1.96(0–13.0)	0.73 (0–10)	0.02
Mean use yrs (users only)	5.62 (1.5–13.0)	4.11 (0.1–10)	0.11
Any Tamoxifen use			
No	66 (29.5%)	951 (92.6%)	
Yes	17 (20.5%)	76 (7.4%)	<0.0001
Mean use yrs (all subjects)	1.14(0–13)	0.41 (0–10)	0.02
Mean use yrs (users only)	5.57 (1.5–13)	3.43 (0.1–10)	0.01
Menopausal status			
Premenopausal	24 (28.9%)	430 (41.9%)	
Postmenopausal	59 (71.1%)	597 (58.1%)	0.02

Variables	Cases N = 83	Controls 83 sets (N = 1027)	P-value
Mean age of menopause	45.5 (18–57)	45.4 (27–58)	0.97
HRT			
No	68 (84.0%)	883 (84.1%)	
Yes	13 (16.1%)	157 (15.9%)	0.96
Formulation			
E alone	2	42	
EP	8	63	
P alone	2	4	
Unknown	0	35	
Other	1	13	
Oophorectomy			
No	66 (80.5%)	736 (72.1%)	
Yes	16 (19.5%)	285 (27.9%)	0.10
Oral contraceptives (ever)			
No	36 (45.6%)	538 (53.8%)	
Yes	43 (54.4%)	462 (46.2%)	0.03
Smoking (ever)			
No	47 (61.8%)	661 (66.8%)	
Yes	29 (38.2%)	325 (33.2%)	0.60
BMI			
At 18	20.8 (8.5–31.3)	21.2 (11.1–69.2)	0.49
At 30	22.3 (8.5–35.2)	22.6 (13.8–54.1)	0.64
At 40	23.0 (8.5–34.2)	24.8 (12.1–61.2)	0.38
Country of residence			
USA	25	215	
Poland	26	478	
Canada	22	240	Matched
Israel	3	37	
Norway	4	53	
Italy	1	1	
China	1	1	
Austria	1	2	

Table 2

Hazard Ratios Associated with Selected Risk factors for Endometrial Cancer, All Subjects

Variables	Univariate OR (95%CI) P-value	Multivariate OR (95%CI) P-value
Age at baseline questionnaire	0.95 (0.90–1.01) 0.11	0.98 (0.92–1.04) 0.52
Parity (mean)	0.92 (0.76–1.12) 0.40	0.92 (0.75–1.13) 0.42
Breast cancer history		
No	NA	NA
Yes		
Tamoxifen (any use)		
No	1	1
Yes	4.22 (1.84–9.69) 0.007	3.50 (1.51–8.10) 0.003
Tamoxifen		
Breast cancer patients only		
No	1.0	1.0
Yes	5.75 (2.25–14.7) 0.0003	6.21 (2.21–17.5) 0.0005
Menopausal status		
Premenopausal	1	1
Postmenopausal	1.47 (0.69–3.12) 0.31	1.42 (0.63–3.21) 0.39
HRT		
No	1	1
Yes	0.87 (0.42–1.81) 0.71	0.73 (0.33–1.63) 0.44
E alone	0.23 (0.03–1.76)0.16	0.23 (0.03–1.78) 0.16
P alone	4.59 (0.80–26.5) 0.09	6.91 (0.99–48.1) 0.05
EP	1.26 (0.51–3.10) 0.62	0.87 (0.31–2.43) 0.79
Oral Contraceptives		
Never	1	1
Ever	1.50 (0.79–2.85) 0.22	1.49 (0.74–2.99) 0.26
Smoking history		
Never	1	1
Ever	1.14 (0.68–1.90) 0.62	1.08 (0.63–1.84) 0.78
BMI18	1.00 (0.93–1.07) 0.93	1.00 (0.90–1.10) 0.93
BMI30	0.99 (0.92–1.06) 0.73	1.03 (0.89–1.18) 0.71
BMI40	0.98 (0.92–1.04) 0.54	0.98 (0.88–1.09) 0.74

Table 3

Hazard Ratios Associated with Selected Risk factors for Endometrial Cancer, BRCA1 carriers only

Variables	Univariate OR (95%CI) P-value	Multivariate OR (95%CI) P-value
Age at baseline questionnaire	0.94 (0.87–1.00) 0.06	0.96 (0.89–1.04) 0.33
Parity (mean)	0.85 (0.67–1.06) 0.15	0.85 (0.67–1.08) 0.18
Tamoxifen (any use)		
No	1	1
Yes	4.49 (1.79–11.3) 0.001	3.66 (1.44–9.31) 0.006
Tamoxifen Breast cancer patients only		
No	1	1
Yes	6.60 (2.22 – 19.5) 0.0007	7.19 (2.11–24.5) 0.002
Menopausal status		
Premenopausal	1	1
Postmenopausal	1.04 (0.47–2.34) 0.92	1.07 (0.45–2.57) 0.87
HRT		
No	1	1
Yes	1.04 (0.44–2.47) 0.93	0.85 (0.32–2.30) 0.75
E	0.48 (0.06–3.66) 0.48	0.52 (0.06–4.23) 0.54
P	7.44 (1.19–46.4) 0.03	16.5 (2.02–134) 0.009
EP	1.30 (0.44–3.83) 0.63	1.77 (0.20–2.98) 0.70
Oral contraceptives		
Never	1	1
Ever	1.34 (0.65–2.74) 0.43	1.23 (0.56–2.69) 0.61
Smoking history		
Never	1	1
Ever	1.41 (0.78–2.55) 0.26	1.23 (0.66–2.28) 0.51
BMI18	1.01 (0.93–1.09) 0.82	1.00 (0.90–1.11) 0.95
BMI30	1.01 (0.93–1.09) 0.80	1.08 (0.94–1.24) 0.27
BMI40	0.98 (0.91–1.05) 0.55	0.94 (0.83–1.05) 0.28

Table 4

Hazard Ratios Associated with Selected Risk factors for Endometrial Cancer, BRCA2 carriers only

Variables	Univariate OR (95%CI) P-value	Multivariate OR (95%CI) P-value
Age at baseline questionnaire	1.00 (0.90–1.13) 0.95	1.06 (0.91–1.24) 0.47
Parity (mean)	1.19 (0.80–1.76) 0.39	1.42 (0.85–2.39) 0.19
Tamoxifen (any use)		
No	1	1
Yes	3.28 (0.52–20.6) 0.21	6.17 (0.42–91.3) 0.18
Tamoxifen Brest cancer patients only		
No	1	1
Yes	3.77 (0.60–23.6) 0.16	19.2 (0.4–1758) 0.20
Menopausal status		
Premenopausal	Not applicable	Not applicable
Postmenopausal		
HRT		
No	1	1
Yes	0.59 (0.15–2.27) 0.44	0.18 (0.02–1.76) 0.14
E	0	0
P	0	0
EP	1.29 (0.26–6.49) 0.76	0.35 (0.02–5.15) 0.44
Oral contraceptives		
No	1	1
Yes	2.45 (0.50–12.1) 0.27	6.19 (0.61–62.6) 0.12
Smoking history		
Never	1	1
Ever	0.60 (0.21–1.77) 0.36	1.26 (0.34–4.74) 0.73
BMI18	0.97 (0.73–1.29) 0.85	0.89 (0.61–1.31) 0.56
BMI30	0.63 (0.40–0.98) 0.04	0.41 (0.18–0.97) 0.04
BMI40	1.32 (1.00–1.75) 0.05	1.61 (1.06–2.45) 0.02