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The association between smoking and cancer incidence in *BRCA1* and *BRCA2* mutation carriers

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Abstract

Tobacco smoke is an established carcinogen, but the association between tobacco smoking and cancer risk in *BRCA* mutation carriers is not clear. The aim of this study was to evaluate prospectively the association between tobacco smoking and cancer incidence in a cohort of *BRCA1* and *BRCA2* mutation carriers. The study population consisted of unaffected *BRCA* mutation carriers. Information on lifestyle including smoking histories, reproductive factors, and past medical histories was obtained through questionnaires. Incident cancers were updated biennially via follow-up questionnaires. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using time-dependent Cox regression models. There were 700 incident cancers diagnosed over 26,711 person-years of follow-up. The most frequent cancers seen in *BRCA* mutation carriers were breast (n = 428; 61%) and ovarian (n = 109; 15%) cancer. Compared to non-smokers, (ever) smoking was associated with a modest increased risk of all cancers combined (HR = 1.17; 95%CI 1.01–1.37). Women in the highest group of total pack-years (4.3–9.8) had an

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increased risk of developing any cancer (HR = 1.27; 95%CI 1.04–1.56), breast cancer (HR=1.33, 95%CI 1.02–1.75), and ovarian cancer (HR = 1.68; 95%CI 1.06–2.67) compared to never smokers. The associations between tobacco smoking and cancer did not differ by *BRCA* mutation type or by age at diagnosis. This prospective study suggests that tobacco smoking is associated with a modest increase in the risks of breast and ovarian cancer among women with *BRCA1* or *BRCA2* mutation.

Keywords

BRCA1; *BRCA2*; smoking; breast cancer; ovarian cancer

Introduction

Cigarette smoking has been categorized as a group 1 carcinogen by the International Agency for Research, in particular for cancers of the lung, bladder, liver, and colon.[1, 2] Although smoking and the risk of developing breast or ovarian cancer is not conclusive, recent meta-analyses of the prospective studies suggest a 13% increased risk of breast cancer (relative risk [RR] = 1.13; 95% confidence intervals [CI] 1.09–1.17) and no increase in the risk of ovarian cancer (RR = 1.06; 95%CI 0.99–1.12) for current smokers compared to never smokers.[3, 4] These risk estimates are derived from studies conducted in the general population.

Women with inherited mutations in *BRCA1* or *BRCA2* face high lifetime risks of developing breast and ovarian and other cancers.[5, 6] The incomplete penetrance of a *BRCA* mutation implies that exogenous factors may modify cancer risk.[7, 8] The identification of modifiable exposures is critical for this high-risk population, given that effective prevention strategies are currently limited to prophylactic surgery. Cigarette smoking is of interest in this respect because it is modifiable. Furthermore, because of the important role of the BRCA proteins in the repair of double stranded DNA breaks as well as damage due to oxidative stress, mutation carriers may be more susceptible to the relevant carcinogens.[9]

It is not clear if cigarette smoking is a risk factor for cancer in this high-risk population. A number of earlier reports, including two from our group, have yielded inconclusive results and have been limited by small sample sizes and retrospective study designs, which are vulnerable to selection bias and information bias.[10–16] We undertook a prospective evaluation of cigarette smoking and overall cancer incidence, as well as breast and ovarian cancer incidence, in a large cohort of *BRCA1* and *BRCA2* mutation carriers.

Materials and Methods

Study population

The study population was selected from a multicenter longitudinal cohort of *BRCA1* and *BRCA2* mutation carriers from 80 participating centers in 17 countries including North America, Europe, Asia, the Caribbean, and Latin America. These women sought genetic testing for a *BRCA1* or *BRCA2* mutation because of a personal or family history of breast and/or ovarian cancer and genetic counselling was conducted for all study subjects (with the

exception of some from the University of Utah and University of California Irvine). Mutation detection was conducted using a range of techniques, but all nucleotide sequences were confirmed by direct sequencing of DNA. Informed consent was obtained from all participants and the study protocol was approved by the institutional ethics review board of each host institution.

Data collection and ascertainment of incident cancers

All study subjects completed a baseline questionnaire at the individual center at the time of a clinic appointment or at their home at a later date. The questionnaire requested information on family and personal history of cancer, reproductive and medical histories, including preventive oophorectomy and mastectomy. Follow-up questionnaires were completed every two years thereafter and administered by mail or completed over the phone by a genetic counsellor or research assistant. At each follow-up, participants provided updates on exposures, preventive surgery and cancer incidence. The questionnaire also collected detailed information on past and current regular cigarette smoking history including: age first started to smoke, age last smoked, and the average number of cigarette packs smoked per week. Incident breast cancers (invasive breast cancer only) and ovarian cancers were identified by self-report, and 85% of breast cancer cases and 63% of ovarian cancer cases were confirmed by review of pathology reports. In the contributing Korean institutions, incident cancer cases were ascertained by the national cancer registry.

Study Subjects Available for Analysis

There were 15,731 women with a *BRCA1* or *BRCA2* mutation who were potentially eligible for inclusion in the current study. Of the 15,731 women, we excluded subjects who had a previous diagnosis of any cancer (n = 8,541), had no information on smoking history (n = 542), or had no follow-up information (n = 2,372). After these exclusions, a total of 4,276 subjects qualified for inclusion in the analysis. For the analysis of tobacco smoking with breast and ovarian cancer, we additionally excluded the subjects who had a prophylactic mastectomy (n = 209) and oophorectomy (n = 854) at baseline, respectively, and we excluded those who had missing information on prophylactic surgery during the follow-up period (n = 147). There was a total of 3,920 subjects in the analysis for breast cancer and 3,275 subjects for ovarian cancer.

Statistical analysis

Time dependent Cox regression analysis was used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) of all cancer as well as breast and ovarian cancer, with smoking. All the smoking exposures, as well as the covariates, included in the analyses were treated as time-dependent variables and updated to reflect the any changes following completion of the baseline questionnaire or at any point in the follow-up. In the analysis of smoking and all cancers (as well as breast cancer specific incidence), the continuous variables of exposures were categorized into quartiles groups based on the distribution in the entire cohort. For the analysis of ovarian cancer, continuous variables of exposures were categorized into 3 groups (never smoker, and dichotomization of exposed group by median) based on the distribution in the entire cohort.

We created the following smoking variables: 1) smoking history (ever, never), 2) current smoking history (non-smoker, past smoker, current smoker), 3) age first started to smoke (never, ≥ 20 years, 18–19 years, ≤ 17 years for overall and breast cancer analysis; never, > 19 years, ≤ 19 years for ovarian cancer analysis), 4) average packs smoked per week (never, ≤ 2 packs, 2 < packs ≤ 5, >5 packs for overall and breast cancer analysis; never, ≤ 3 packs, > 3 packs for ovarian cancer analysis), 5) smoking duration (never, ≤ 8 years, 8 < years ≤ 18, >18 years for overall and breast cancer analysis; never, ≤ 10 years, > 10 years for ovarian cancer analysis), and 6) total pack-years (never, ≤ 2.3 pack-years, 2.3 < pack-years ≤ 9.8, > 9.8 pack-years for overall and breast cancer analysis; never, ≤ 4.3 pack-years, > 4.3 pack-years for ovarian cancer analysis). Total pack-years smoked was estimated by the following equation: (cigarette packs smoked per day) × (total years smoked). 7) duration of smoking before first birth among parous women (never smoker, smoking initiation after first birth, ≤ 5 years, and > 5 years). For the analysis of overall cancer incidence, participants were followed from the date of baseline questionnaire until either the: 1) date of completion of the last follow-up questionnaire, 2) date of cancer diagnosis, or 3) date of death. For the analysis of breast cancer incidence, participants were followed from the date of baseline questionnaire until either the: 1) date of completion of the last follow-up questionnaire, 2) date of breast cancer or ovarian cancer diagnosis, 3) date of prophylactic mastectomy, or 4) date of death and similarly for ovarian cancer incidence except for censoring at date of prophylactic oophorectomy instead of date of prophylactic mastectomy.

The multivariate model was adjusted for age (continuous), country of residence (Canada and United States/Europe/others [including Asia and Latin America]), *BRCA* mutation type (*BRCA1* or *BRCA2*), pregnancy history (ever/never), oral contraceptive use (ever/never), regular alcohol consumption (ever/never) and obesity (normal, less than 25 kg/m^2/ overweight, 25–29.9 kg/m^2/obese, 30 kg/m^2 or more). We also performed analyses stratified by *BRCA1* and *BRCA2* mutation, age at breast cancer diagnosis (<50 vs. ≥50 years), and ER status of breast cancer cases.

The *P* for trend was estimated by treating the numerical values of the categorical variables as a score in time-dependent Cox regression model to assess dose-response relationships. All analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC, USA) and a *P* value less than 0.05 was considered as statistical significance.

Results

A total of 4,276 women with a *BRCA1* or *BRCA2* mutation were included in the current prospective analysis. The age-adjusted baseline characteristics by smoking history are shown in Table 1. Women who smoked were, on average, older (40.4 years vs. 38.1 years), more likely to be *BRCA1* mutation carriers (78% vs. 21%), to have been pregnant (43% vs. 31%), and to have breastfed for a longer duration (compared to women who never smoked (all comparisons $P < 0.01$). Smokers were more likely to have used oral contraceptives (42% vs. 36%), to have a greater BMI (mean 24.7 vs. 24.0 kg/m^2), to live in Europe (54% vs. 43%), to consume alcohol (45% vs. 28%) and to consume coffee regularly (46% vs. 24%) compared with never smokers (all comparisons $P < 0.01$).

Average follow up time for smokers and nonsmokers was 6.5 and 6.1 years, respectively. Average age at diagnosis of any cancer for smokers and nonsmokers was 49.3 and 47.4 years old, respectively. During the entire follow-up period of 26,711 person-years, 700 incident cancers were identified. These are summarized by *BRCA* mutation type in Supplemental table 1. Among the 3,256 *BRCA1* mutation carriers, there were 544 incident cancers and among the 987 *BRCA2* mutation carriers, there were 153 incident cancers. The most commonly diagnosed cancers in *BRCA* mutation carriers were breast cancer (n=339; 10.4% in *BRCA1* mutation carriers and n=87; 8.8% in *BRCA2* mutation carriers) and ovarian cancer (n=103; 3.2% in *BRCA1* mutation carriers and n=6; 0.6% in *BRCA2* mutation carriers). Other commonly diagnosed cancers included ductal carcinoma *in situ* or lobular carcinoma *in situ*, as well as cancers of the skin, peritoneal and fallopian tube. With respect to smoking related cancers, there were nine pancreatic cancers, seven lung cancers and one bladder cancer diagnosed in the entire cohort.

The association between cigarette smoking and the risk of developing cancer at any site is shown in Table 2. Ever smokers had a 17% increased risk of developing any cancer compared to never smokers (HR=1.17; 95% CI 1.01–1.37). Current smokers had a 31% increased risk of developing cancer compared to never smokers (HR=1.31; 95% CI 1.07–1.59; *P* trend = 0.01). Earlier age at first smoking was associated with a significant increasing risk of developing cancer compared to never smoking (*P*-trend = 0.03). Increasing duration of smoking was associated with a significant increasing risk of developing cancer compared to never smoking (*P*-trend < 0.01). Women in the highest category of total pack-years of smoking (i.e., >9.8) had a 27% increased risk of cancer compared to women who never smoked (HR=1.27; 95% CI 1.04–1.56; *P* -trend = 0.02). Average packs of cigarette smoked per week (*P*-trend = 0.13) were not associated with the risk of any cancer.

Table 3 summarizes the results for the analysis of cigarette smoking and breast cancer risk. Ever smoking was not significantly associated with the risk of breast cancer (HR = 1.16; 95%CI 0.96–1.41). Current smokers had a 28% increased risk of breast cancer compared to never smokers (HR=1.28; 95% CI 1.00–1.64; *P* -trend = 0.07). Women in the highest quartile of smoking duration had a 34% increased risk of developing breast cancer compared to women who never smoked (HR=1.34; 95% CI 1.04–1.73; *P* -trend = 0.02). Women in the highest quartile of total pack-years had a 33% increased risk of developing breast cancer compared to never smokers (HR=1.33; 95% CI 1.02–1.75; *P*-trend = 0.08). There was no significant association between age at smoking initiation (*P*-trend = 0.39), duration of smoking before the first birth among parous women (*P*-trend = 0.77) or average packs smoked per week (*P*-trend = 0.22) and the risk of developing breast cancer.

Past smokers had a 69% increased risk of developing ovarian cancer compared to never smokers (HR 1.69; 95% CI 1.06–2.71)(Table 4). Current smoking was not significantly associated with risk (HR = 1.25; 95%CI 0.73–2.12). Women who smoked for 10 or more years had a 63% increased risk of developing ovarian cancer compared to women who never smoked (HR=1.63; 95% CI 1.04–2.54). Total pack-years of more than 4.3 was associated with the increased risk of ovarian cancer compared with never smoking (HR=1.68; 95% CI 1.06–2.67). There was a significant dose-response relationship between both smoking duration and total pack-years and the risk of developing ovarian cancer (*P*-trend = 0.03).

The associations between tobacco smoking and overall cancer, as well as breast and ovarian cancer were similar in analyses stratified by *BRCA* mutation type (*P* heterogeneity > 0.05, Supplementary tables 2–4) and age at diagnosis (*P* heterogeneity > 0.05; data not shown).

Discussion

In this prospective evaluation of cigarette smoking and cancer risk among women with an inherited *BRCA1* or *BRCA2* mutation, we observed a borderline significant increased risk of developing any cancer, as well as breast and ovarian cancer specifically, with a history of smoking. Compared to never smokers, both increasing duration of smoking and pack-years of smoking were associated with a significant 1.3-fold increased risk of all cancers and of breast cancer, as well as a 1.6-fold increased risk of ovarian cancer. Although we found no significant associations between age at first use or average packs smoked per week, there was a consistent and significant dose-response relationship between lifetime dose of smoking (measured as total pack-years) and long-term exposure (measured as duration of smoking) with cancer risk. The results from this large prospective analyses implicate smoking as a likely carcinogen in this high-risk population, which we estimate confers a 30% and 60% increased risk of developing *BRCA*-associated breast and ovarian cancer, respectively.

Among studies conducted in the general population, causal links between cigarette smoking and 17 different types of cancers of the lung, bladder, liver, colorectal cancer has previously confirmed.[2] Although the number of smoking-related cancers in the current study was low, we observed a 1.3-fold increased risk of cancer overall with smoking history (including duration of smoking and total pack-years) which is in accordance with risk estimates from epidemiologic reports stemming from women in the general population. To our knowledge, there are no prior evaluations of smoking and total *BRCA*-cancer incidence.

Although the evidence on tobacco smoking for breast cancer is not sufficient to infer a causal relationship in general population, a recent meta-analysis of the prospective studies estimated a significant 13% increased risk of breast cancer with current smoking (summary RR = 1.13; 95% CI 1.09–1.17).[3] The observed adverse effect of smoking was greater than this in our cohort of high-risk women, which current smoking was associated with 28% increased risk of breast cancer. Also we observed a 33%-34% increased risk of *BRCA*-associated breast cancer with increasing duration and pack-years. A retrospective cohort study of smoking and cancer in *BRCA* mutation carriers, which included 990 women, reported a 2.1-fold increased risk of breast cancer among women with more than 20 pack-years of smoking.[15] Limitations of the latter analysis is that follow-up was initiated at birth and women were followed until a cancer diagnosis or the date of interview and prevalent cases were included.

Our current findings contrast with our earlier reports that similarly assessed the association between smoking and breast cancer among *BRCA* mutation carriers (a subset of which were also included in the current analysis).[12, 13] In the first report by our group which included 186 matched cases and controls, we reported a significant reduction in *BRCA*-breast cancer risk among women who smoked more than four pack-years (odds ratio [OR] = 0.46; 95% CI

0.27–0.80).[14] In an updated analysis with a substantially larger number of *BRCA* mutation carriers (1,097 matched cases and controls), Ghadirian *et al.*, found no association between smoking and the risk of breast cancer compared to never smoking (OR for ever smoking = 1.05; 95% CI 0.88–1.25 and OR for > 20 pack-years = 0.81; 95% CI 0.57–1.15).[12] Finally, in our most recent report with 2,538 matched pairs, ever smoking were not associated with the risk of breast cancer regardless of *BRCA1* or *BRCA2* mutation, although a past history of smoking was associated with a significantly increased risk of breast cancer among *BRCA1* carriers but not *BRCA2* mutation carriers.[13]

In a small retrospective cohort study of *BRCA1* mutation carriers (176 cases and 140 non-cases), ever smoking was associated with a decreased risk of breast cancer (HR = 0.63; 95% CI 0.47–0.87) and this inverse association was attenuated in the women with a 28 repeat allele for steroid receptor co-activator gene *AIB1* (hazard ratio = 0.19; 95% CI 0.07–0.54).[11] A case-control study composed of *BRCA* mutation aged less than 50 years old with reported that smoking history and high pack-years of smoking were associated with an increased risk of breast cancer with an estimated average of 7% increase per pack-year of smoking in *BRCA* mutation carriers.[10] These prior reports were retrospective analyses and limited by a relatively smaller number of *BRCA* mutation carriers. Furthermore, in the case-control studies published by our team, there was an average of eight years between the date of diagnosis to date of interview or genetic testing, and thus, the analyses were vulnerable to survival and recall bias.

A recent pooled analysis in the general population from 14 cohort studies found an 18% increased risk of developing breast cancer among women who smoked 10 or more years prior to their first pregnancy compared to women who never smoked (HR = 1.18; 95% CI 1.12–1.24).[17] Duration of smoking before the first birth among parous women was emerging risk factor for breast cancer in relation to the timing of smoking initiation.[18, 19] Given the early age at breast cancer onset among *BRCA* mutation carriers (between ages 30 and 50), it is plausible that early exposures may significantly impact risk. Thus, we also evaluated the effect of smoking by age at first use, duration of smoking before first birth, and age at diagnosis; however, we found no evidence for an effect of this classification of smoking exposure on risk. Our study showed that heavy smoking with long time exposure was the important attributor in the development of breast cancer regardless of exposure timing, diagnosed age for breast cancer, and *BRCA* mutation type.

We observed a borderline significant 1.6-fold increased risk of ovarian cancer among women in the highest tertile of both smoking duration and total pack-years compared to never smokers. One other study has evaluated the relationship between smoking and ovarian cancer among *BRCA* mutation carriers.[20] In this matched case-control study of Polish women with *BRCA1* mutations (150 cases and 150 controls), smoking was not associated with ovarian cancer (OR = 1.3; 95% CI 0.8–2.3).[20] Among women in the general population the relationship between smoking and ovarian cancer varies by histologic subtype; current smoking is associated with an increased risk of mucinous ovarian cancer compared to never smoking (RR=1.79; 95% CI 1.47–2.17), a decreased risk of endometrioid ovarian cancer (RR=0.81; 95% CI 0.70–0.94)[4] but is not associated with the serous subtype (RR=0.99; 95% CI 0.91–1.08) or the clear-cell subtype (RR=0.80; 95% CI 0.63–1.01) in meta-analysis from

51 studies. Histologically, mucinous ovarian cancer are similar to cancers of the intestinal epithelium, which are also well-known smoking-related cancer.[2] The findings from studies of women in the general population (who are likely not mutation carriers) contrasts with our current findings given that *BRCA*-ovarian cancers are predominantly of the serous or endometrioid subtypes.[4, 21]

Tobacco contains more than 7,000 chemical compounds including benzo[a]pyrene, hydrocarbons, tobacco-specific nitrosamines, benzene, formaldehyde, carbon monoxide cyanide, and polonium, the majority of which are well-established carcinogens and toxins.[16] These components of tobacco smoke have been shown to contribute to carcinogenesis via multiple pathways, including DNA binding and consequent induction of mutation, inflammation, oxidative stress, and epigenetic mechanisms.[22] Given the important role of the *BRCA* proteins in the repair of double-stranded DNA breaks, this population of women may be more susceptible to damage caused which could be caused from oxygen species by smoking[23] The underlying mechanisms to explain the carcinogenic effects of cigarette smoking for breast cancer include the detection of circulating metabolites such as polycyclic aromatic hydrocarbons, aromatic amines, and N-nitrosamines in breast tissue and p53 mutation.[24, 25] In contrast, anti-carcinogenic effects of smoking for breast cancer have also been suggested because of the anti-estrogenic effects of tobacco[26, 27] Specifically, smoking has been shown to have inverse association with mammographic density which is a biomarker of breast cnacer.[28, 29]

Our study had several limitations including the ascertainment of incident cancers via questionnaire and our inability to confirm all reported cancers by medical record review. Although this may have resulted in misclassification of the outcome variables, self-report of cancer incidence has previously been shown to be valid and reliable, particularly for breast cancer.[30–32] The sensitivity of self-reported cancer in women has been estimated between 0.61 and 0.89, while the sensitivity for breast cancer (the major incident cancer in our population) is high (range 0.85–0.91).[30–32] Loss to follow-up is inevitable in prospective studies and can result in selection bias attributed to differences in the distribution of the exposure variable among subjects with and without follow-up information.[33] In our study population, we did not have follow-up information on 36 % (2,372 subjects of 6,648 subjects) of the baseline participants, and thus, we could not ascertain the cancer incidence. Nevertheless, the proportion study subjects with follow-up information did not differ by smoking status in our population of *BRCA* mutation carriers (i.e., 66% in ex-smokers or current smokers) vs. 63% in never smokers. Also we could not find obvious association in the stratified analysis because of small sample size.

Despite these limitations, the current study had several strengths including the large sample of *BRCA* mutation carriers (n = 4,276) with a relatively long follow-up period (median = 5.4 years and interquartile range = 3.1 to 8.8 years). The prospective nature of our study design allowed for data collection prior to disease incidence, minimizing both selection and information bias. We reduced the influence of measurement error by using biennial follow-up questionnaires to update both exposures and covariates.

In conclusion, findings from this large prospective analysis of smoking and *BRCA*-associated cancers clearly implicates smoking as a risk factor, particularly for breast and ovarian cancer, the most common type of cancers diagnosed in this high-risk population. The adverse health effects of smoking should be discussed by clinicians and genetic counsellors managing women with *BRCA*-associated cancers. The impact of smoking on cancers incidence in male *BRCA* mutation carriers warrants further study.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Novelty Impact Statement

Findings from this large prospective analysis of smoking and *BRCA*-associated cancers clearly implicates smoking as a risk factor, particularly for breast and ovarian cancer, the most common type of cancers diagnosed in this high-risk population. The adverse health effects of smoking should be discussed by clinicians and genetic counsellors managing women with *BRCA*-associated cancers. The impact of smoking on cancers incidence in male *BRCA* mutation carriers warrants further study.

Table 1

Baseline characteristics of *BRCA* mutation carriers by smoking status

Variables	Non-smoker (n=2,566)	Smoker (n=1,710)	*P*-value*
Age, years (mean ± SD)	38.1 ± 12.6	40.4 ± 11.6	< 0.01
BMI, kg/m^2 (mean ± SD)	24.0 ± 4.8	24.7 ± 5.0	< 0.01
Country, n (%)			
US/Canada	1,248 (48.6)	747 (43.7)	
Europe	1,113 (43.4)	923 (54.0)	
The others	205 (8.0)	40 (2.3)	< 0.01
BRCA mutation, n (%)			
BRCA1 mutation	1,918 (74.8)	1,338 (78.3)	
BRCA2 mutation	627 (24.4)	360 (21.1)	
BRCA1 and *BRCA2* mutation or unknown	21 (0.8)	12 (0.7)	< 0.01
Pregnancy history, n (%)			
Never	781 (30.5)	349 (20.5)	
Ever	1,782 (69.5)	1,357 (79.5)	< 0.01
Breastfeeding duration, n (%)			
Never	1,033 (44.6)	624 (40.1)	
Less than 6 months	430 (18.6)	398 (25.6)	
More than 6 months	854 (36.9)	533 (34.3)	< 0.01
Menarche age, n (%)			
≤ 13 years	886 (35.6)	581 (34.7)	
14 years	713 (28.6)	467 (27.9)	
≥15 years	892 (35.8)	627 (37.4)	0.75
Menopausal status, n (%)			
Premenopausal	1,841 (72.1)	1,114 (65.2)	
Postmenopausal	711 (27.9)	596 (34.8)	0.40
Oral contraceptive use, n (%)			
Never	1,027 (40.2)	576 (33.9)	
Ever	1,529 (59.8)	1,121 (66.1)	< 0.01
HRT use, n (%)			
Never	2,192 (86.1)	1,398 (82.7)	
Ever	354 (13.9)	292 (17.3)	0.37
Tamoxifen use, n (%)			
Never	2,325 (97.8)	1,619 (98.0)	
Ever	51 (2.2)	33 (2.0)	0.21
Regular alcohol drinker, n (%)			
No	867 (34.3)	339 (20.2)	
Yes	1,661 (65.7)	1,340 (79.8)	< 0.01
Regular coffee consumer, n (%)			
No	818 (34.2)	253 (15.6)	
Yes	1,574 (65.8)	1,365 (84.4)	< 0.01

Variables	Non-smoker (n=2,566)	Smoker (n=1,710)	*P*-value*
Prophylactic mastectomy history, n (%)			
No	2,407 (95.1)	1,589 (94.9)	
Yes	123 (4.9)	86 (5.1)	0.95
Oophorectomy history, n (%)			
No	2,063 (81.2)	1,325 (77.9)	
Yes	477 (18.8)	377 (22.1)	0.75

* adjusted for age using logistic regression

BMI, body mass index; HRT, hormone replacement therapy

Table 2

Association between smoking and risk of all cancer incidence among *BRCA* mutation carriers

	Person-years (Total 26,711)	Incident cases (N = 700)	Crude HR (95% CI)	Adjusted HR* (95% CI)
Smoking history				
Never	15,335	359	Reference	Reference
Ever	11,377	341	1.28 (1.11–1.49)	1.17 (1.01–1.37)
Current smoking history				
Past smoker	6,243	184	1.27 (1.06–1.51)	1.09 (0.91–1.31)
Current smoker	5,050	153	1.29 (1.07–1.56)	1.31 (1.07–1.59)
		P for trend =	< 0.01	0.01
Age at first smoking				
≥ 20 years	3,767	115	1.31 (1.06–1.61)	1.08 (0.87–1.34)
18–19 years	3,129	93	1.27 (1.01–1.60)	1.20 (0.95–1.51)
≤ 17 years	4,247	119	1.20 (0.98–1.48)	1.22 (0.99–1.51)
		P for trend =	< 0.01	0.03
Average packs smoked/week				
<2 packs	3,006	80	1.14 (0.90–1.46)	1.09 (0.85–1.39)
2 ≤ packs < 5	3,757	101	1.15 (0.92–1.43)	1.10 (0.88–1.38)
5 ≤ packs	3,685	115	1.34 (1.08–1.65)	1.17 (0.95–1.45)
		P for trend =	0.01	0.13
Smoking duration				
≤ 8 years	3,796	70	0.79 (0.61–1.02)	0.88 (0.68–1.14)
8 < duration ≤ 18	3,400	93	1.17 (0.93–1.47)	1.18 (0.93–1.48)
18 < duration	3,968	166	1.80 (1.50–2.17)	1.37 (1.13–1.66)
		P for trend =	< 0.01	< 0.01
Total pack-years				
≤ 2.3 pack-years	3,424	71	0.89 (0.69–1.15)	0.96 (0.75–1.25)
2.3< pack-years ≤ 9.8	3,342	91	1.16 (0.92–1.46)	1.12 (0.89–1.41)
> 9.8 pack-years	3,534	131	1.59 (1.30–1.95)	1.27 (1.04–1.56)
		P for trend =	< 0.01	0.02

*adjusted for age, country, *BRCA* mutation, pregnancy history, contraceptive drug use, alcohol drinking and obesity using time-dependent Cox regression model

Table 3

Association between smoking and risk of breast cancer among *BRCA* mutation carriers

	Person-years (Total 21,098)	Incident cases (N = 420)	Crude HR (95% CI)	Adjusted HR* (95% CI)
Smoking history				
Never	11,990	217	Reference	Reference
Ever	9,108	203	1.22 (1.01–1.48)	1.16 (0.96–1.41)
Current smoking history				
Past smoker	4,835	104	1.16 (0.92–1.47)	1.04 (0.82–1.32)
Current smoker	4,250	95	1.24 (0.98–1.58)	1.28 (1.00–1.64)
		P for trend =	0.06	0.07
Age at first smoking				
≥ 20 years	3,165	75	1.29 (0.99–1.67)	1.15 (0.88–1.51)
18–19 years	2,584	52	1.10 (0.82–1.49)	1.08 (0.79–1.47)
≤ 17 years	3,223	65	1.11 (0.84–1.45)	1.12 (0.84–1.48)
		P for trend =	0.34	0.39
Average packs smoked/week				
<2 packs	2,413	47	1.06 (0.77–1.45)	1.04 (0.76–1.43)
2 ≤ packs < 5	3,086	59	1.05 (0.79–1.41)	1.04 (0.77–1.39)
5 ≤ packs	2,783	67	1.32 (1.01–1.74)	1.22 (0.92–1.61)
		P for trend =	0.08	0.22
Smoking duration				
≤ 8 years	3,050	39	0.71 (0.50–0.99)	0.76 (0.54–1.07)
8 < duration ≤ 18	2,750	60	1.20 (0.90–1.60)	1.21 (0.90–1.61)
18 < duration	3,172	93	1.59 (1.24–2.02)	1.34 (1.04–1.73)
		P for trend =	< 0.01	0.02
Total pack-years				
≤ 2.3 pack-years	2,800	43	0.84 (0.61–1.17)	0.89 (0.64–1.24)
2.3< pack-years ≤ 9.8	2,680	51	1.05 (0.77–1.42)	1.01 (0.74–1.38)
> 9.8 pack-years	2,720	76	1.53 (1.18–1.98)	1.33 (1.02–1.75)
		P for trend =	0.01	0.08
Duration of smoking before the first birth among parous women				
Never smoker	7,905	168	Reference	Reference
Initiation after first birth	952	27	1.33 (0.88–1.99)	1.29 (0.85–1.96)
≤ 5 years	2,606	48	0.86 (0.63–1.19)	0.86 (0.62–1.19)
> 5 years	2,858	69	1.14 (0.86–1.50)	1.12 (0.84–1.50)
		P for trend =	0.69	0.77

*adjusted for age, country, *BRCA* mutation, pregnancy history, contraceptive drug use, alcohol drinking and obesity using time-dependent Cox regression model

Table 4

Association between smoking and risk of ovarian cancer among *BRCA* mutation carriers

	Person-years (Total 15,720)	Incident cases (N = 100)	Crude HR (95% CI)	Adjusted HR* (95% CI)
Smoking history				
Never	9,260	49	Reference	Reference
Ever	6,460	51	1.48 (1.00–2.19)	1.45 (0.96–2.19)
Current smoking history				
Past smoker	3,036	30	1.84 (1.16–2.90)	1.69 (1.06–2.71)
Current smoker	3,375	21	1.17 (0.70–1.96)	1.25 (0.73–2.12)
		P for trend =	0.25	0.22
Age at first smoking				
> 19 years	2,531	30	2.22 (1.41–3.50)	1.69 (1.05–2.72)
≤ 19 years	3,627	19	0.98 (0.58–1.66)	1.18 (0.68–2.05)
		P for trend =	0.52	0.28
Average packs smoked/week				
≤ 3 packs	3,417	27	1.48 (0.93–2.37)	1.72 (1.05–2.81)
3 packs <	2,700	19	1.30 (0.76–2.20)	1.17 (0.68–2.01)
		P for trend =	0.20	0.33
Smoking duration				
≤ 10 years	3,205	15	0.88 (0.50–1.58)	1.22 (0.67–2.22)
10 years <	3,154	36	2.12 (1.38–3.27)	1.63 (1.04–2.54)
		P for trend =	< 0.01	0.03
Total pack-years				
≤ 4.3 pack-years	3,187	14	0.83 (0.46–1.50)	1.11 (0.60–2.04)
4.3 pack-years <	2,871	32	2.06 (1.32–3.22)	1.68 (1.06–2.67)
		P for trend =	0.01	0.03

*adjusted for age, country, *BRCA* mutation, pregnancy history, contraceptive drug use, and alcohol drinking using time-dependent Cox regression model