Published OnlineFirst December 2, 2019; DOI: 10.1158/1055-9965.EPI-19-0546

Alcohol Consumption, Cigarette Smoking, and Risk of Breast Cancer for *BRCA1* and *BRCA2* Mutation Carriers: Results from The BRCA1 and BRCA2 Cohort Consortium

Hongyan Li[1], Mary Beth Terry[2,3], Antonis C. Antoniou[4], Kelly-Anne Phillips[5,6,7], Karin Kast[8,9,10], Thea M. Mooij[11], Christoph Engel[12]; Catherine Noguès[13], Dominique Stoppa-Lyonnet[14,15], Christine Lasset[16], Pascaline Berthet[17], Veronique Mari[18], Olivier Caron[19]; for the GENEPSO study; Daniel Barrowdale[4], Debra Frost[4], Carole Brewer[20], D. Gareth Evans[21], Louise Izatt[22], Lucy Side[23], Lisa Walker[24], Marc Tischkowitz[25], Mark T. Rogers[26], Mary E. Porteous[27], Katie Snape[28]; for the EMBRACE study; Hanne E.J. Meijers-Heijboer[29], Johan J.P. Gille[29], Marinus J. Blok[30], Nicoline Hoogerbrugge[31]; for the HEBON Investigators; Mary B. Daly[32], Irene L. Andrulis[33,34], Saundra S. Buys[35], Esther M. John[36]; Sue-Anne McLachlan[37,38], Michael Friedlander[39,40]; for the kConFab Investigators; Yen Y. Tan[41], Ana Osorio[42], Trinidad Caldes[43], Anna Jakubowska[44,45], Jacques Simard[46], Christian F. Singer[41], Edith Olah[47], Marie Navratilova[48], Lenka Foretova[48], Anne-Marie Gerdes[49], Marie-José Roos-Blom[11], Brita Arver[50,51], Håkan Olsson[51], Rita K. Schmutzler[52,53], John L. Hopper[5], Roger L. Milne[5,54,55], Douglas F. Easton[4,56], Flora E. Van Leeuwen[11], Matti A. Rookus[11], Nadine Andrieu[57,58,59,60], and David E. Goldgar[1,61]

ABSTRACT

Background: Tobacco smoking and alcohol consumption have been intensively studied in the general population to assess their effects on the risk of breast cancer, but very few studies have examined these effects in *BRCA1* and *BRCA2* mutation carriers. Given the high breast cancer risk for mutation carriers and the importance of *BRCA1* and *BRCA2* in DNA repair, better evidence on the associations of these lifestyle factors with breast cancer risk is essential.

Methods: Using a large international pooled cohort of *BRCA1* and *BRCA2* mutation carriers, we conducted retrospective (5,707 *BRCA1* mutation carriers and 3,525 *BRCA2* mutation carriers) and prospective (2,276 *BRCA1* mutation carriers and 1,610 *BRCA2* mutation carriers) analyses of alcohol and tobacco consumption using Cox proportional hazards models.

Results: For both *BRCA1* and *BRCA2* mutation carriers, none of the smoking-related variables was associated with breast cancer risk, except smoking for more than 5 years before a first full-term pregnancy (FFTP) when compared with parous women who never smoked. For *BRCA1* mutation carriers, the HR from retrospective analysis (HR_R) was 1.19 [95% confidence interval (CI), 1.02–1.39] and the HR from prospective analysis (HR_P) was 1.36 (95% CI, 0.99–1.87). For *BRCA2* mutation carriers, smoking for more than 5 years before an FFTP showed an association of a similar magnitude, but the confidence limits were wider (HR_R = 1.25; 95% CI, 1.01–1.55 and HR_P = 1.30; 95% CI, 0.83–2.01). For both carrier groups, alcohol consumption was not associated with breast cancer risk.

Conclusions: The finding that smoking during the prereproductive years increases breast cancer risk for mutation carriers warrants further investigation.

Impact: This is the largest prospective study of *BRCA* mutation carriers to assess these important risk factors.

[1]Huntsman Cancer Institute, University of Utah School of Medicine, Salt Lake City, Utah. [2]Department of Epidemiology, Columbia University, New York, New York. [3]Herbert Irving Comprehensive Cancer Center, Columbia University Medical Center, New York, New York. [4]Centre for Cancer Genetic Epidemiology, Department of Public Health and Primary Care, Strangeways Research Laboratory, Worts Causeway, University of Cambridge, Cambridge, United Kingdom. [5]Centre for Epidemiology and Biostatistics, School of Population and Global Health, The University of Melbourne, Victoria, Australia. [6]The Sir Peter MacCallum Department of Oncology, University of Melbourne, Parkville, Australia. [7]Department of Medical Oncology, Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia. [8]Department of Gynecology and Obstetrics, Medical Faculty and University Hospital Carl Gustav Carus, Technische Universität, Dresden, Germany. [9]National Center for Tumor Diseases (NCT), Partner Site Dresden, Germany. [10]German Cancer Consortium (DKTK), Dresden and German Cancer Research Center (DKFZ), Heidelberg, Germany. [11]Department of Epidemiology, Netherlands Cancer Institute, Amsterdam, the Netherlands. [12]Institute for Medical Informatics, Statistics and Epidemiology, University of Leipzig, Germany. [13]Institut Paoli-Calmettes, Département d'Anticipation et de Suivi des Cancers, Oncogénétique Clinique and Aix Marseille Univ, INSERM, IRD, SESSTIM, Marseille, France. [14]Institut Curie, Service de Génétique Médicale, Paris, France. [15]Inserm, U830, Université Paris Descartes, Paris, France. [16]Unité de prévention et Epidémiologie Génétique, Centre Léon Bérard - Lyon/UMR CNRS 5558, Université de Lyon – Lyon, France. [17]Département de biopathologie, Oncogénétique clinique, Centre François Baclesse – Caen, France. [18]CLCC Antoine Lacassagne, Département d'Hématologie - Oncologie médicale, Nice, France. [19]Département de Médecine, Gustave Roussy Hôpital Universitaire – Villejuif, France. [20]Department of Clinical Genetics, Royal Devon & Exeter Hospital, Exeter, United Kingdom. [21]Genomic Medicine, NIHR Manchester Biomedical Research Centre, Manchester Academic Health Sciences Centre, Division of Evolution and Genomic Sciences, Manchester University, Manchester University Hospitals NHS Foundation Trust, Manchester, United Kingdom. [22]Clinical Genetics, Guy's and St. Thomas' NHS Foundation Trust, London, United Kingdom. [23]Wessex Clinical Genetics Service, The Princess Anne Hospital, Southampton, United Kingdom. [24]Oxford Regional Genetics Service, Churchill Hospital, Oxford, United Kingdom. [25]University of Cambridge Department of Medical Genetics, NIHR Cambridge Biomedical Research Centre, and Cancer Research UK

Published OnlineFirst December 2, 2019; DOI: 10.1158/1055-9965.EPI-19-0546

Introduction

Carriers of pathogenic variants (mutations) in the *BRCA1* and *BRCA2* genes are at very high risk of developing breast cancer and ovarian cancer. We recently reported cumulative risks of breast cancer to 80 years of 72% [95% confidence interval (CI), 65%–79%] for *BRCA1* mutation carriers and 69% (95% CI, 61%–77%) for *BRCA2* mutation carriers based on prospective follow-up of unaffected female mutation carriers (1). However, the associations of lifestyle risk factors on breast cancer risk for *BRCA1* and *BRCA2 (BRCA1/2)* mutation carriers remain uncertain. The Oxford collaborative reanalysis of 53 epidemiologic studies concluded that for women unselected for family history, alcohol consumption was associated with increased breast cancer risk, while there was no association between smoking and breast cancer risk (2). However, some recent studies have found that breast cancer risk may be increased if smoking starts early in life, that is, before menarche or a first full-term pregnancy (FFTP; refs. 3–5). Of the studies that have attempted to identify lifestyle factors that modify breast cancer risk for *BRCA* mutation carriers, few have examined associations with smoking or alcohol consumption and the results are inconsistent (6–15), possibly due to methodologic limitations and small sample sizes. In view of the very high breast cancer risk for *BRCA1/2* mutation carriers, together with the well-known carcinogenic and mutagenic activity of alcohol metabolites (16) and tobacco components (17), and the widespread consumption of alcohol and tobacco, it is important to derive reliable estimates of the associations of alcohol and tobacco consumption with breast cancer risk for *BRCA1* and *BRCA2* mutation carriers. Moreover, given the role of BRCA1 and BRCA2 in DNA repair, it is plausible that smoking and alcohol consumption could have a disproportionate effect for mutation carriers at least in terms of absolute risk. Furthermore, recent experimental data have shown a haploinsufficiency for BRCA2 and a replication fork instability in *BRCA2* heterozygous cells induced by acetaldehyde, an endogenous product of alcohol catabolism (18).

To provide more reliable estimates of the associations of these lifestyle factors with breast cancer risk for mutation carriers, we analyzed data from the largest available cohort of nearly 10,000 *BRCA1* and *BRCA2* mutation carriers (1) and compared the results from this prospective analysis with the results from the retrospective analysis from same cohort.

Materials and Methods

Study design

We harmonized risk factor and follow-up data from three prospective cohorts: The International BRCA1/2 Carrier Cohort Study (IBCCS; ref. 19), the Kathleen Cuningham Foundation Consortium for Research Into Familial Breast Cancer (kConFab) Follow-Up Study (20, 21), and the Breast Cancer Family Registry (BCFR; ref. 22). The combined cohort ("The BRCA1 and BRCA2 Cohort Consortium") included data from 21 centers in Western countries (Supplementary Table S1). The total cohort enrolled 9,845 *BRCA1* and *BRCA2* mutation carriers ages 18–80 years (after excluding 14 carriers of a mutation in both genes; refs. 19, 23). Sixty-six percent of the study participants were enrolled in one of the five ongoing nationwide studies in the United Kingdom and Ireland [Epidemiological Study of Familial Breast Cancer (EMBRACE)], France [Gene Etude Prospective Sein Ovaire (GENEPSO)], the Netherlands [Hereditary Breast and Ovarian cancer study Netherlands (HEBON)], Australia and New Zealand (kConFab), or Austria [Medical University of Vienna (MUV)]. The other studies were based on regional clinical genetic centers or were population based (three centers of the BCFR).

Cambridge Center, Cambridge Biomedical Campus, Cambridge, United Kingdom. [26]All Wales Medical Genetics Services, University Hospital of Wales, Cardiff, United Kingdom. [27]South East of Scotland Regional Genetics Service, Western General Hospital, Edinburgh, United Kingdom. [28]Medical Genetics Unit, St. George's, University of London, London, United Kingdom. [29]Department of Clinical Genetics, VU University Medical Center, Amsterdam, the Netherlands. [30]Department of Clinical Genetics, Maastricht University Medical Center, Maastricht, the Netherlands. [31]Department of Human Genetics, Radboud University Medical Center, Nijmegen, the Netherlands. [32]Department of Clinical Genetics, Fox Chase Cancer Center, Philadelphia, Pennsylvania. [33]Department of Molecular Genetics, University of Toronto, Toronto, Ontario, Canada. [34]Lunenfeld-Tanenbaum Research Institute, Sinai Health System, Toronto, Ontario, Canada. [35]Department of Medicine, University of Utah Health Sciences Center, Huntsman Cancer Institute, Salt Lake City, Utah. [36]Stanford University School of Medicine, Department of Medicine, Division of Oncology, and Stanford Cancer Institute, Stanford University School of Medicine, Stanford, California. [37]Department of Medicine, St. Vincent's Hospital, The University of Melbourne, Parkville, Victoria, Australia. [38]Department of Medical Oncology, St. Vincent's Hospital, Fitzroy, Victoria, Australia. [39]Department of Medical Oncology, Prince of Wales Hospital, Randwick, New South Wales, Australia. [40]Division of Cancer Medicine, Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia. [41]Department of OB/GYN and Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria. [42]Human Genetics Group, Spanish National Cancer Centre (CNIO) and Biomedical Network on Rare Diseases (CIBERER), Madrid, Spain. [43]Molecular Oncology Laboratory, Hospital Clinico San Carlos, IdISSC, CIBERONC (ISCIII), Madrid, Spain. [44]Department of Genetics and Pathology, Pomeranian Medical University, Unii Lubelskiej 1, Szczecin, Poland. [45]Independent Laboratory of Molecular Biology and Genetic Diagnostics, Pomeranian Medical University, Szczecin, Poland. [46]Genomics Center, Centre Hospitalier Universitaire de Québec – Université Laval Research Center, Quebec City, Quebec, Canada. [47]Department of Molecular Genetics, National Institute of Oncology, Budapest, Hungary. [48]Department of Cancer Epidemiology and Genetics, Masaryk Memorial Cancer Institute, Zluty kopec 7, Brno, Czech Republic. [49]The Department of Oncology and Pathology, Karolinska Institute, Stockholm, Sweden. [50]Department of Clinical Genetics, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark. [51]Department of Oncology, Lund University Hospital, Lund, Sweden. [52]Center for Familial Breast and Ovarian Cancer, Center for Integrated Oncology (CIO), Medical Faculty, University Hospital Cologne, Cologne, Germany. [53]Center for Molecular Medicine Cologne (CMMC), University of Cologne, Cologne, Germany. [54]Division of Cancer Epidemiology and Intelligence, Cancer Council Victoria, Melbourne, Australia. [55]Precision Medicine, School of Clinical Sciences at Monash Health, Monash University, Clayton, Victoria, Australia. [56]Centre for Cancer Genetic Epidemiology, Department of Oncology, Strangeways Research Laboratory, Worts Causeway, University of Cambridge, Cambridge, United Kingdom. [57]INSERM, U900, Paris, France. [58]Institut Curie, Paris, France. [59]Mines Paris Tech, Fontainebleau, France. [60]PSL Research University, Paris, France. [61]Department of Dermatology, University of Utah School of Medicine, Salt Lake City, Utah.

Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

N. Andrieu and D.E. Goldgar are co-senior authors for this article.

Corresponding Authors: David E. Goldgar, University of Utah School of Medicine, 30 N. Medical Drive, Salt Lake City, UT 84132. Phone: 801-581-6465; Fax: 801-581-6484; E-mail: david.goldgar@hsc.utah.edu; and Nadine Andrieu, Cancer Genetic Epidemiology Team, INSERM Unit 900, Institut Curie, 26 rue d'Ulm, 75005 Paris, France. Phone: 3301-7238-9383; E-mail: nadine.andrieu@curie.fr

Cancer Epidemiol Biomarkers Prev 2020;29:368–78

doi: 10.1158/1055-9965.EPI-19-0546

Published OnlineFirst December 2, 2019; DOI: 10.1158/1055-9965.EPI-19-0546

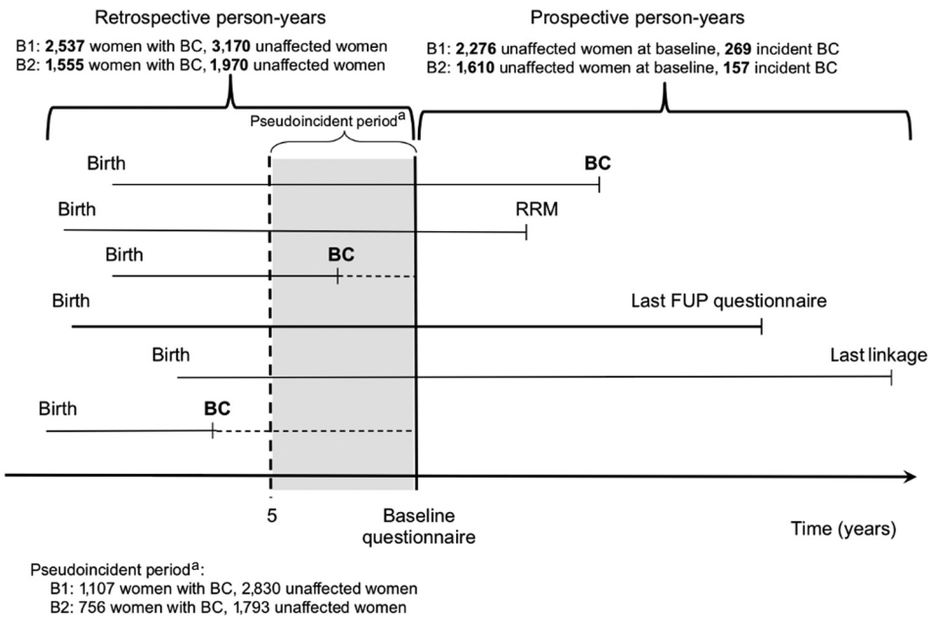

Figure 1.
Design of The BRCA1 and BRCA2 Cohort Consortium. Each line represents a sample IBCCS-BCFR-KConFab participant from birth to censure: a diagnosis of primary breast cancer; an RRM; a last FUP questionnaire; and the most recent information from an external source (last linkage). B1, *BRCA1*; B2, *BRCA2*; BC, breast cancer; FUP, follow-up; RRM, risk-reducing mastectomy.

Study participants and data collection

Women were eligible for this analysis if they were 18–80 years of age and had tested positive for a pathogenic *BRCA1* or *BRCA2* mutation. The total group with follow-up for a first breast cancer and eligible for retrospective or prospective analyses consisted of 9,845 women (9,232 for retrospective and 3,886 for prospective analysis), including 6,032 *BRCA1* and 3,813 *BRCA2* mutation carriers (**Fig. 1**). Women who were unaffected with breast cancer at baseline were excluded from prospective analyses if either: they had ovarian cancer (415 *BRCA1* carriers and 142 *BRCA2*); other cancer (146 *BRCA1* and 141 *BRCA2*); risk-reducing mastectomy (RRM; 298 *BRCA1* and 139 *BRCA2*); or did not have follow-up data (360 *BRCA1*; 226 *BRCA2*). Participants provided written informed consent and each study was approved by the relevant ethical committee. Study participants were invited to complete a baseline questionnaire at enrollment and regular follow-up questionnaires. The questionnaires requested detailed information on known or suspected risk factors for breast and ovarian cancer. The primary sources of information on cancer occurrence were: self-report via questionnaire only (six studies, 8% of the study group), self-report with medical record validation (two studies, 37%), medical records (four studies, 18%), and linkage to cancer registries (four studies, 37%), although some studies had a mix of these diagnostic sources. Information on vital status was obtained from municipal or death registries or from contact with family members.

Assessment of alcohol consumption and cigarette smoking

We collected information on ever smoking (defined as at least one pack of cigarettes per month for 1 year), current smoking intensity (average number of cigarettes per day), age started smoking, age stopped smoking, and total duration of smoking (in years) and average number of cigarettes per day during this period. Questionnaires also asked about ever alcohol use (at least one glass per month for 1 year), alcohol use in the last year (i.e., current use), and total years of consumption. In most studies, separate questions were asked about types of alcohol and for each type the amount consumed per week. Some studies asked about alcohol use at age 20 years; women in studies without this information (e.g., BCFR) were treated as missing for variables related to alcohol consumption at age 20 years.

After data harmonization across studies, smoking variables were converted to ever/never smoking, number of cigarettes per day (current or past for ex-smokers) in five categories (0; 1–5, 6–10, 11–20, and >20), years of smoking and estimated number of pack-years in three categories (<1, 1–20, and >20), age started in three categories ($\leq$15, 16–19, and $\geq$20 years), and timing relative to their FFTP. Alcohol variables were converted to ever/never, and total average number of standard drinks per day at age 20 years and in the year prior to completing the questionnaire.

Statistical analysis

To assess the association between alcohol and tobacco consumption and the risk of breast cancer, we used Cox proportional hazards regression models. Women were eligible for prospective analyses if they were free of cancer and had no history of RRM at the start of follow-up (enrollment/baseline questionnaire or mutation test, whichever came last); for participants recruited in a research setting, follow-up was considered to begin at enrollment. The primary endpoint was breast cancer [invasive ($n = 393$) or *in situ* ($n = 33$) for the prospective analyses] diagnosed more than 1 month after enrollment. The censoring event was the first of diagnosis of primary breast cancer (invasive or *in situ*), diagnosis of another cancer, RRM, last questionnaire, last information from external source (e.g., linkage), loss to follow-up, age 80 years, or death. Alcohol and tobacco variables were analyzed as fixed in the models because timing of changes in consumption was too uncertain to generate time-dependent variables. Analyses were adjusted for alcohol consumption (ever vs. never) when tobacco consumption was analyzed and for smoking (ever vs. never) when alcohol consumption was analyzed. Because the consumption of alcoholic beverages and tobacco consumption might interact with other breast cancer risk factors (24, 25), we also performed analyses adjusted on additional potential confounders like, age at menarche (<12, $\geq$12–<13, $\geq$13–<14, $\geq$14–<15, and $\geq$15 years, age missing, or never had menstrual period), age at FFTP (<30 and $\geq$30+nulliparous),

Published OnlineFirst December 2, 2019; DOI: 10.1158/1055-9965.EPI-19-0546

Table 1. Characteristics of the *BRCA1* mutation carriers.

	Women with breast cancer		Unaffected women	
	Retrospective ($N = 2,537$) *N*(%) or Mean ± SD	Prospective ($N = 269$) *N*(%) or Mean ± SD	Retrospective ($N = 3,170$) *N*(%) or Mean ± SD	Prospective ($N = 2,007$) *N*(%) or Mean ± SD
Age at entry		40.7 ± 10.3		37.5 ± 11.8
Age at censure	40.1 ± 8.8	44.9 ± 10.3	39.3 ± 11.6	43.1 ± 12.3
Year of birth				
<1950	804 (31.7)	35 (13.0)	527 (16.6)	205 (10.2)
1950–1959	842 (33.2)	76 (28.3)	647 (20.4)	347 (17.3)
1960–1969	662 (26.1)	104 (38.7)	946 (29.8)	586 (29.2)
≥1970	229 (9.0)	54 (20.1)	1,050 (33.1)	869 (43.3)
Study group				
EMBRACE	743 (29.3)	41 (15.2)	817 (25.8)	432 (21.5)
GENEPSO	324 (12.8)	46 (17.1)	692 (21.8)	442 (22.0)
HEBON	337 (13.3)	40 (14.9)	465 (14.7)	202 (10.1)
KConFab		55 (20.4)		270 (13.5)
BCFR	456 (18.0)	50 (18.6)	433 (13.7)	277 (13.8)
Others[a]	677 (26.7)	37 (13.8)	763 (24.1)	384 (19.1)
Smoking/alcohol status				
Never	567 (22.3)	64 (23.8)	698 (22.0)	457 (22.8)
Ever, alcohol only	773 (30.5)	65 (24.2)	976 (30.8)	618 (30.8)
Ever, smoking only	281 (11.1)	29 (10.8)	306 (9.7)	193 (9.6)
Ever, smoking and alcohol	891 (35.1)	104 (38.7)	1,146 (36.2)	713 (35.5)
Missing	25 (1.0)	7 (2.6)	44 (1.4)	26 (1.3)
Smoking status				
Never	1,344 (53.0)	132 (49.1)	1,688 (53.2)	1,081 (53.9)
Past smoker	809 (31.9)	71 (26.4)	883 (27.9)	504 (25.1)
Current smoker	364 (14.3)	63 (23.4)	565 (17.8)	398 (19.8)
Missing	20 (0.8)	3 (1.1)	34 (1.1)	24 (1.2)
Cigarettes per day (current or past)				
0	1,344 (53.0)	132 (49.1)	1,688 (53.2)	1,081 (53.9)
≤5	266 (10.5)	32 (11.9)	366 (11.5)	237 (11.8)
6–10	311 (12.3)	34 (12.6)	414 (13.1)	259 (12.9)
11–20	417 (16.4)	49 (18.2)	482 (15.2)	294 (14.6)
>20	86 (3.4)	14 (5.2)	80 (2.5)	58 (2.9)
Missing	113 (4.5)	8 (3.0)	140 (4.4)	78 (3.9)
Number of pack-years				
<1	1,387 (54.7)	138 (51.3)	1,774 (56.0)	1,147 (57.1)
1–20	722 (28.5)	96 (35.7)	976 (30.8)	628 (31.3)
>20	281 (11.1)	26 (9.7)	238 (7.5)	132 (6.6)
Missing	147 (5.8)	9 (3.3)	182 (5.7)	100 (5.0)
Age started smoking (years)				
Never	1,344 (53.0)	132 (49.1)	1,688 (53.2)	1,081 (53.9)
≤15	233 (9.2)	33 (12.3)	364 (11.5)	240 (12.0)
16–19	487 (19.2)	69 (25.7)	576 (18.2)	385 (19.2)
≥20	190 (7.5)	15 (5.6)	194 (6.1)	106 (5.3)
Missing	283 (11.2)	20 (7.4)	348 (11.0)	195 (9.7)
Glasses of alcohol per day in past year[b]				
0	1,017 (40.1)	108 (40.1)	1,222 (38.5)	772 (38.5)
<1	830 (32.7)	72 (26.8)	955 (30.1)	560 (27.9)
1–2	430 (16.9)	48 (17.8)	588 (18.5)	391 (19.5)
>2	93 (3.7)	12 (4.5)	217 (6.8)	143 (7.1)
Missing	167 (6.6)	29 (10.8)	188 (5.9)	141 (7.0)
Glasses of alcohol per day at age 20 years				
0	804 (31.6)	65 (24.2)	992 (31.3)	520 (25.9)
<1	670 (26.4)	41 (15.2)	785 (24.8)	421 (21.0)
1–2	292 (11.5)	22 (8.2)	470 (14.8)	269 (13.4)
>2	64 (2.5)	9 (3.4)	183 (5.8)	111 (5.5)
Missing	707 (27.9)	132 (49.1)	740 (23.3)	686 (34.2)

[a]Others included the following studies (total number): MUV-Austria (261), MODSQUAD (228), GC-HBOC (178), Lund-BRCA (160), OUH (105), HCSC (84), INHERIT (66), NIO-Hungry (98), IHCC (97), Stockholm-BRCA (71), CNIO (40), Milan Italy (33), HSP (9), DKFZ (4), Belgium (3), and Dusseldorf Germany (3).
[b]Year preceding completion of last questionnaire.

Published OnlineFirst December 2, 2019; DOI: 10.1158/1055-9965.EPI-19-0546

Table 2. Characteristics of the *BRCA2* mutation carriers.

	Women with breast cancer		Unaffected women	
	Retrospective (*N* = 1,555) *N*(%) or Mean ± SD	Prospective (*N* = 157) *N*(%) or Mean ± SD	Retrospective (*N* = 1,970) *N*(%) or Mean ± SD	Prospective (*N* = 1,453) *N*(%) or Mean ± SD
Age at start		45.1 ± 10.1		40.0 ± 12.6
Age at censure	43.4 ± 9.1	49.0 ± 10.3	41.4 ± 12.4	45.0 ± 13.0
Year of birth				
<1950	563 (36.2)	42 (26.8)	386 (19.6)	200 (13.8)
1950–1959	510 (32.8)	44 (28.0)	388 (19.7)	259 (17.8)
1960–1969	385 (24.8)	55 (35.0)	572 (29.0)	433 (29.8)
≥1970	97 (6.2)	16 (10.2)	624 (31.7)	561 (38.6)
Study group				
EMBRACE	611 (39.3)	42 (26.8)	744 (37.8)	441 (30.4)
GENEPSO	161 (10.4)	18 (11.5)	437 (22.2)	307 (21.1)
HEBON	90 (5.8)	4 (2.5)	147 (7.5)	71 (4.9)
KConFab		38 (24.2)		250 (17.2)
BCFR	359 (23.1)	33 (21.0)	322 (16.3)	222 (15.3)
Others[a]	334 (21.5)	22 (14.0)	320 (16.2)	162 (11.1)
Smoking/alcohol status				
Never	321 (20.6)	44 (28.0)	440 (22.3)	361 (24.8)
Ever, alcohol only	486 (31.3)	41 (26.1)	632 (32.1)	459 (31.6)
Ever, smoking only	134 (8.6)	13 (8.3)	154 (7.8)	110 (7.6)
Ever, smoking and alcohol	597 (38.4)	56 (35.7)	722 (36.6)	512 (35.2)
Missing	17 (1.1)	3 (1.9)	22 (1.1)	11 (0.8)
Smoking status				
Never	808 (52.0)	85 (54.1)	1,079 (54.8)	824 (56.7)
Past smoker	514 (33.1)	47 (29.9)	544 (27.6)	357 (24.6)
Current smoker	218 (14.0)	21 (13.4)	334 (17.0)	264 (18.2)
Missing	15 (1.0)	4 (2.5)	13 (0.7)	8 (0.6)
Cigarettes per day (current or past)				
0	808 (52.0)	85 (54.1)	1,079 (54.8)	824 (56.7)
≤5	158 (10.2)	15 (9.6)	212 (10.8)	154 (10.6)
6–10	202 (13.0)	24 (15.3)	232 (11.8)	173 (11.9)
11–20	262 (16.8)	19 (12.1)	316 (16.0)	214 (14.7)
>20	55 (3.5)	7 (4.5)	59 (3.0)	49 (3.4)
Missing	70 (4.5)	7 (4.5)	72 (3.7)	39 (2.7)
Number of pack-years				
<1	846 (54.4)	90 (57.3)	1,126 (57.2)	862 (59.3)
1–20	430 (27.7)	44 (28.0)	578 (29.3)	434 (29.9)
>20	197 (12.7)	16 (10.2)	179 (9.1)	111 (7.6)
Missing	82 (5.3)	7 (4.5)	87 (4.4)	46 (3.2)
Age at start smoking (years)				
Never	808 (52.0)	85 (54.1)	1,079 (54.8)	824 (56.7)
≤15	136 (8.7)	19 (12.1)	228 (11.6)	148 (10.2)
16–19	302 (19.4)	23 (14.6)	358 (18.2)	290 (20.0)
≥20	153 (9.8)	20 (12.7)	154 (7.8)	102 (7.0)
Missing	156 (10.0)	10 (6.4)	151 (7.7)	89 (6.1)
Glasses of alcohol per day past year[b]				
0	596 (38.3)	68 (43.3)	754 (38.3)	568 (39.1)
<1	574 (36.9)	41 (26.1)	605 (30.7)	420 (28.9)
1–2	280 (18.0)	30 (19.1)	375 (19.0)	264 (18.2)
>2	57 (3.7)	7 (4.5)	166 (8.4)	118 (8.1)
Missing	48 (3.1)	11 (7.0)	70 (3.6)	83 (5.7)
Glasses of alcohol per day at age 20 years				
0	424 (27.3)	31 (19.7)	592 (30.1)	345 (23.7)
<1	439 (28.2)	32 (20.4)	489 (24.8)	283 (19.5)
1–2	201 (12.9)	15 (9.6)	337 (17.1)	219 (15.1)
>2	56 (3.6)	3 (1.9)	132 (6.7)	89 (6.1)
Missing	435 (28.0)	76 (48.4)	420 (21.3)	517 (35.6)

[a]Others included the following studies (total number): MUV-Austria (100), MODSQUAD (80), GC-HBOC (105), Lund-BRCA (58), OUH (62), HCSC (65), INHERIT (74), NIO-Hungry (31), IHCC (0), Stockholm-BRCA (13), CNIO (44), Milan Italy (12), and HSP (10).
[b]Year preceding completion of last questionnaire.

Published OnlineFirst December 2, 2019; DOI: 10.1158/1055-9965.EPI-19-0546

number of full-term pregnancies (0, 1, and ≥2), body mass index (<18.5, 18.5–24.9, 25–29.9, 30 kg/m^{2}or greater, and missing), oral contraceptive use (ever, never, and missing), bilateral oophorectomy (yes and no), and number of affected relatives with breast cancer (0, 1, ≥2, and unknown). We conducted separate analyses for *BRCA1* and *BRCA2* mutation carriers. We stratified for birth cohort and study and used robust variance estimation to account for familial clustering.

Table 3. Association of alcohol and tobacco consumption with breast cancer risk for *BRCA1* mutation carriers, retrospective (weighted) and prospective analyses.

	Retrospective HR[a] (95% CI)	*P*	Prospective HR[b] (95% CI)	*P*
Smoking/alcohol status				
Never	1.00		1.00	
Ever, alcohol only	1.04 (0.89–1.22)	0.63	0.89 (0.61–1.28)	0.52
Ever, smoke only	1.13 (0.92–1.38)	0.25	0.89 (0.57–1.38)	0.59
Ever, smoke and alcohol	1.04 (0.89–1.22)	0.59	1.16 (0.81–1.65)	0.41
Cigarettes per day[c] (current or past)				
0	1.00		1.00	
≤5	1.01 (0.85–1.21)	0.91	1.25 (0.85–1.85)	0.26
6–10	1.01 (0.85–1.20)	0.91	1.06 (0.73–1.54)	0.75
11–20	1.11 (0.95–1.29)	0.20	1.19 (0.86–1.66)	0.30
>20	1.16 (0.87–1.55)	0.32	1.26 (0.70–2.27)	0.44
Continuous (missing excluded)[c]	1.00 (1.00–1.01)	0.15	1.01 (1.00–1.02)	0.22
Number of pack-years[c]				
<1			1.00	
1–20			1.21 (0.92–1.58)	0.17
>20			1.20 (0.78–1.85)	0.40
Continuous (missing excluded)[c]			1.01 (1.00–1.02)	0.12
Age at start smoking (years)[c]				
Never	1.00		1.00	
≤15	1.10 (0.90–1.34)	0.34	1.11 (0.75–1.63)	0.60
16–19	1.09 (0.94–1.27)	0.25	1.27 (0.93–1.72)	0.13
≥20	1.02 (0.83–1.25)	0.88	1.10 (0.65–1.86)	0.73
Age at start for parous women (years)[c]				
Never	1.00		1.00	
≤15	1.10 (0.89–1.36)	0.37	1.18 (0.79–1.76)	0.42
16–19	1.12 (0.96–1.32)	0.16	1.24 (0.90–1.73)	0.19
≥20	1.03 (0.83–1.29)	0.77	1.04 (0.57–1.89)	0.90
Age at start for nulliparous women (years)[c]				
Never	1.00		1.00	
≤15	1.28 (0.75–2.19)	0.37	1.22 (0.40–3.68)	0.73
16–19	0.94 (0.64–1.39)	0.76	1.15 (0.48–2.71)	0.76
≥20	0.86 (0.50–1.49)	0.59	1.80 (0.61–5.31)	0.29
Smoking and parity[c]				
Never smoke and parous	1.00		1.00	
Never smoke and nulliparous	1.31 (1.08–1.60)	0.01	0.70 (0.46–1.07)	0.10
Ever smoke and nulliparous	1.31 (1.05–1.62)	0.02	0.80 (0.49–1.31)	0.38
Ever smoke and parous				
5 years or less before FFTP	1.01 (0.85–1.20)	0.91	1.11 (0.75–1.66)	0.60
>5 years before FFTP	1.19 (1.02–1.39)	0.03	1.36 (0.99–1.87)	0.06
Glasses of alcohol last year per day[d]				
0			1.00	
<1			0.99 (0.73–1.35)	0.95
1–2			1.06 (0.76–1.49)	0.74
>2			0.93 (0.50–1.72)	0.82
Continuous (per glass)[d]			1.02 (0.86–1.21)	0.84
Glasses of alcohol per day[d] at age 20				
0	1.00		1.00	
<1	1.00 (0.87–1.16)	0.95	0.93 (0.62–1.39)	0.71
1–2	0.89 (0.74–1.07)	0.21	0.92 (0.57–1.51)	0.75
>2	0.59 (0.43–0.81)	0.001	1.35 (0.67–2.72)	0.40
Continuous (per glass)[d]	0.88 (0.80–0.96)	0.004	1.04 (0.84–1.28)	0.71

[a]Stratified on birth cohort and five study groups for the retrospective analyses.
[b]Stratified on birth cohort and six study groups for the prospective analyses.
[c]Adjusted for alcohol consumption (ever vs. never).
[d]Adjusted for tobacco consumption (ever vs. never).

Published OnlineFirst December 2, 2019; DOI: 10.1158/1055-9965.EPI-19-0546

In addition to the prospective analysis, we conducted full-cohort retrospective analyses, in which follow-up was assumed to start at birth and women were followed until the first of diagnosis of primary breast cancer (invasive or *in situ*), diagnosis of another cancer, RRM, start of prospective follow-up (baseline questionnaire or mutation test, whichever came last), or age 80 years. Thus, there was no overlap in follow-up period for individual women included in the retrospective and prospective analyses. Because of nonrandom sampling of prevalent cases of breast cancer, all analyses of retrospective data were performed using the weighted regression approach described by Antoniou and colleagues (26). Because changes in habits might occur after a breast cancer diagnosis, the number of glasses per day consumed during the last year and the number of pack years at the date of baseline questionnaire were not included in the retrospective analyses.

To minimize potential survival bias, we also conducted an additional retrospective analysis of a pseudoincident cohort, which was defined as follow-up starting 5 years before enrollment/baseline questionnaire, and thus only included cases diagnosed within the 5 years prior to enrolment.

Analyses were stratified by birth cohort into four groups ($\leq$1950, 1951–1959, 1960–1968, and $\geq$1969 for retrospective analyses and $\leq$1957, 1958–1966, 1967–1974, and $\geq$1975 for prospective analyses). We also assessed associations by birth cohort and study. All statistical analyses were performed using STATA (version 14, StataCorp).

Results

Tables 1 and **2** summarize the descriptive statistics of the two cohorts of *BRCA1* and *BRCA2* mutation carriers, respectively. Comparison of the retrospective and prospective analysis identified differences in distributions of cigarette consumption: we observed more ex-smokers and never smokers (i.e., noncurrent smokers) in the retrospective analysis than in the prospective analysis for both *BRCA1* (84.9% vs. 75.5% for cases and 81.1% vs. 79.0% for unaffected women) and *BRCA2* (85.0% vs. 84.1% for cases and 82.4 % vs. 81.3% for unaffected women) mutation carriers.

BRCA1 mutation carriers

For *BRCA1* mutation carriers, there were no associations between breast cancer risk and the alcohol measures examined, except for reduced risk associated with higher alcohol consumption in the retrospective analysis, with an HR_R of 0.59 (95% CI, 0.43–0.81; $P = 0.001$) for more than two glasses of alcohol consumed at age 20 years when compared with zero glasses of alcohol (**Table 3**). However, no associations were observed with alcohol consumption at age 20 years or at baseline in the prospective analyses.

There were no associations with ever smoking, number of cigarettes smoked, pack-years, or age at start smoking, in either the prospective or retrospective analysis. However, among parous women, increased breast cancer risk was associated with more than 5 years of smoking before their FFTP in both prospective and retrospective analyses when compared with parous women who never smoked ($HR_R = 1.19$; 95% CI, 1.02–1.39 and $HR_P = 1.36$; 95% CI, 0.99–1.87, respectively). Among nulliparous women, there was no evidence of an association with ever smoking when compared with never smoking ($HR_R = 0.97$; 95% CI, 0.74–1.27 and $HR_P = 1.20$; 95% CI, 0.68–2.12). **Figure 2** displays the cumulative risks of breast cancer for women who smoked for more than 5 years before their FFTP compared with parous never smokers for *BRCA1* mutation carriers.

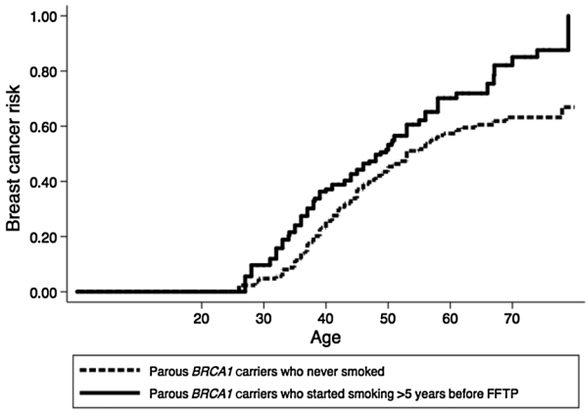

Figure 2.
Cumulative risk of breast cancer for never smoking parous women and those who smoked for more than 5 years before the FFTP among *BRCA1* mutation carriers (prospective analysis).

BRCA2 mutation carriers

Both, ever use of smoking and alcohol drinking were associated with increased breast cancer risk when compared with women who neither smoked nor drank alcohol for *BRCA2* mutation carriers, but only in the retrospective analysis (ever alcohol consumption in nonsmokers $HR_R = 1.32$; 95% CI, 1.03,1.70; $P = 0.03$ and ever smoking in nondrinkers $HR_R = 1.37$; 95% CI, 1.00–1.89; $P = 0.05$), ever alcohol and ever smoking (i.e., at least one glass per month for 1 year plus at least one pack of cigarettes per month for 1 year; $HR_R = 1.43$; 95% CI, 1.13–1.81; $P = 0.003$; **Table 4**). Similar to the findings for *BRCA1* mutation carriers, in both prospective and retrospective analyses we observed an increased breast cancer risk associated with having smoked more than 5 years before a FFTP ($HR_R = 1.25$; 95% CI, 1.01–1.55 and $HR_P = 1.30$; 95% CI, 0.83–2.02, respectively), but the estimates were statistically significant only in the retrospective analysis.

Sensitivity analyses

Results from retrospective analyses that used the pseudoincident cohort were consistent with those from the full-cohort retrospective analyses, except for *BRCA1* mutation carriers where smoking more than 5 years before a FFTP point estimate slightly lowered and significance disappeared (Supplementary Data, Supplementary Table S2). We observed no significant heterogeneity in the HRs for smoking more than 5 years before a FFTP (Supplementary Figs. S1 and S2), with the exception of heterogeneity by birth cohort for the prospective analysis for *BRCA1* mutation carriers which is due to the most recent birth cohort where the HR_P was high, although bounded by a large CI (see Supplementary Fig. S2A). There was no significant heterogeneity by study group with regard to the association we observed for high alcohol consumption in the retrospective analysis for *BRCA1* or *BRCA2* mutation carriers ($P = 0.19$ and 0.14, respectively; data not shown).

In our primary analyses, we did not adjust the analyses for other possible confounders because most of the other risk factors for breast cancer are unlikely to be correlated with the primary alcohol and smoking exposures of interest. The multivariable-adjusted results are presented in Supplementary Tables S3 and S4. As expected, multivariable adjustment did not materially change the

Published OnlineFirst December 2, 2019; DOI: 10.1158/1055-9965.EPI-19-0546

Table 4. Association of alcohol and tobacco consumption with breast cancer risk for *BRCA2* mutation carriers, retrospective (weighted) and prospective analyses.

	Retrospective HR[a] (95% CI)	*P*	Prospective HR[b] (95% CI)	*P*
Smoking/alcohol status				
Never	1.00		1.00	
Ever, alcohol only	1.32 (1.03–1.70)	0.03	0.77 (0.49–1.20)	0.25
Ever, smoking only	1.37 (1.00–1.89)	0.05	0.77 (0.39–1.50)	0.44
Ever, smoking and alcohol	1.43 (1.13–1.81)	0.003	0.98 (0.64–1.52)	0.94
Cigarettes per day[c]				
0	1.00		1.00	
≤5	1.08 (0.85–1.37)	0.52	1.06 (0.60–1.85)	0.85
6–10	1.22 (0.97–1.54)	0.08	1.75 (1.11–2.75)	0.02
11–20	1.21 (0.98–1.51)	0.08	0.85 (0.51–1.43)	0.55
>20	0.97 (0.65–1.43)	0.87	0.74 (0.33–1.69)	0.48
Number of pack-years[c]				
<1			1.00	
1–20			1.20 (0.82–1.76)	0.34
>20			0.92 (0.53–1.60)	0.76
Continuous (missing excluded)[c]			1.00 (0.98–1.01)	0.75
Age at start smoking (years)[c]				
Never	1.00		1.00	
≤15	1.15 (0.87–1.50)	0.32	1.23 (0.74–2.06)	0.43
16–19	1.29 (1.06–1.58)	0.01	0.79 (0.50–1.26)	0.33
≥20	0.97 (0.76–1.25)	0.84	1.73 (1.06–2.85)	0.03
Age at start for parous women years)[c]				
Never	1.00			
≤15	1.22 (0.92–1.63)	0.17	1.31 (0.75–2.27)	0.34
16–19	1.27 (1.02–1.58)	0.03	0.78 (0.48–1.27)	0.32
≥20	0.93 (0.71–1.22)	0.61	1.71 (1.01–2.90)	0.05
Age at start for nulliparous women (years)[c]				
Never	1.00		1.00	
≤15	0.83 (0.26–1.91)	0.66	1.20 (0.28–5.05)	0.81
16–19	1.67 (1.00–2.77)	0.05	0.88 (0.16–4.90)	0.88
≥20	1.76 (0.91–3.39)	0.09	1.19 (0.24–5.76)	0.83
Smoking and parity[c]				
Never smoke and parous	1.00		1.00	
Never smoke and nulliparous	1.13 (0.87–1.48)	0.37	0.82 (0.45–1.49)	0.51
Ever smoke and nulliparous	1.37 (1.02–1.83)	0.04	0.76 (0.35–1.69)	0.51
Ever smoke and parous				
5 years or less before FFTP	1.04 (0.84–1.29)	0.72	0.97 (0.59–1.59)	0.89
>5 years before FFTP	1.25 (1.01–1.55)	0.04	1.30 (0.83–2.01)	0.25
Glasses of alcohol last year per day[d]				
0			1.00	
<1			0.86 (0.57–1.29)	0.46
1–2			1.03 (0.66–1.60)	0.91
>2			0.99 (0.46–2.16)	0.98
Continuous (per glass)[d]			0.93 (0.75–1.17)	0.55
Glasses of alcohol at age 20 years per day[d]				
0	1.00		1.00	
<1	1.19 (0.98–1.44)	0.08	1.17 (0.70–1.95)	0.55
1–2	0.97 (0.76–1.23)	0.80	1.09 (0.57–2.08)	0.79
≥2	0.95 (0.65–1.39)	0.79	0.62 (0.18–2.13)	0.45
Continuous (per glass)[d]	1.02 (0.91–1.14)	0.76	0.95 (0.72–1.26)	0.73

[a]Stratified on birth cohort and five study groups for the retrospective analyses.
[b]Stratified on birth cohort and five study groups for the prospective analyses.
[c]Adjusted for alcohol consumption (ever vs. never).
[d]Adjusted for tobacco consumption (ever vs. never).

HR estimates and more importantly, the overall conclusions of the study.

We performed separate analyses for *BRCA1* and *BRCA2* cohorts based on the hypothesis that the role of the two genes may be different in response to carcinogens from alcohol and tobacco. However, we also performed a pooled analysis which, again, did not change drastically our initial findings nor our conclusions (Supplementary Table S5).

Published OnlineFirst December 2, 2019; DOI: 10.1158/1055-9965.EPI-19-0546

Discussion

Using data from the largest international cohort of *BRCA1* and *BRCA2* mutation carriers, we examined associations with alcohol consumption and smoking separately, using both independent retrospective and prospective data. We found no evidence of an overall association between cigarette consumption with breast cancer risk, except for the *BRCA2* mutation carriers in the retrospective analysis. However, among parous women, we observed that mutation carriers who smoked more than 5 years before their FFTP had a significantly increased risk of breast cancer. This association was seen in both prospective and retrospective analyses, and was seen for both *BRCA1* and *BRCA2* mutation carriers, although the confidence limits for *BRCA2* mutation carriers were wider. The consistency of these findings for mutations carriers of either gene, as well as similar point estimates between prospective and retrospective analyses support the overall conclusion that this time window prior to breast tissue differentiation from pregnancies may be a particularly sensitive window for environmental carcinogenesis.

Unlike in the general population (2, 27) and in accordance with other studies on *BRCA1* and *BRCA2* mutation carriers (6, 28), our findings do not support a positive association between alcohol intake and breast cancer risk, although power was somewhat limited to detect the relatively modest association observed in prior studies (3, 27).

Findings from studies that have examined associations between smoking and breast cancer risk for *BRCA1* and *BRCA2* mutation carriers have been inconsistent. Some reported a null association (12–15), two reported a negative association (9, 10), and two reported a positive association (8, 13), although the latter study showed this association only for *BRCA1* mutation carriers with a history of smoking (13). While retrospective studies have the advantage of larger size and full life history of smoking, prospective studies have the advantage that reporting of behaviors is not influenced by disease.

In our study, women with *BRCA1* mutations who drank more than two glasses of alcohol per day were at decreased breast cancer risk, but only in the retrospective analyses. This discrepancy in results between the two designs for heavier consumers might be explained by survival bias. While tobacco consumption has been suggested as a poor prognostic factor, particularly for women with a diagnosis of triple-negative and luminal A–like breast tumors (29), the association of alcohol with prognosis is less clear. Regular drinking of 0.5 standard drinks or more per day has been shown to be associated with higher risk of breast cancer recurrence, particularly among postmenopausal women (30). Therefore, if women who are heavy consumers are more likely to die after a diagnosis of breast cancer than nondrinking women with breast cancer, the inclusion of prevalent cases in a retrospective analysis may bias results toward unity or even lead to an artefactual negative association (8).

Major strengths of our study include the large sample size for both retrospective and prospective cohorts with very good follow-up and the largest number of *BRCA1* and *BRCA2* prospective mutation carrier breast cancer cases studied to date. Potential weaknesses include the fact that information on alcohol intake and tobacco consumption was self-reported with accompanying potential exposure misclassification and the potential for the retrospective analyses to be affected by survival bias due to the inclusion of prevalent cases. However, the prospective part of our study minimized recall and survival biases.

As in the general population (5), we found a consistent association of increased breast cancer risk with cigarette smoking for mutation carriers who smoked for more than 5 years before their FFTP. The period preceding a FFTP has been shown to be a critical period for breast carcinogenesis (31, 32), particularly for women with a mutation in *BRCA1* or *BRCA2* (33), and potentially even more so for women who accumulated DNA defects during the years before a FFTP because of smoking (**Fig. 2**).

With the exception of the association with smoking for more than 5 years before a FFTP, no associations were found for most smoking-related variables for either *BRCA1* or *BRCA2* mutation carriers. Similarly, no association with alcohol consumption was found in the prospective analysis. However, associations with these two lifestyle factors might be complex and need more detailed information on consumption (e.g., quantities and calendar years of starting and stopping) and timing to be able to prospectively investigate them as time-dependent exposures, and extended follow-up might shed further light upon associations of smoking and alcohol with breast cancer risk for *BRCA1* and *BRCA2* mutation carriers.

In summary, we found no substantial association of breast cancer risk with alcohol consumption or smoking except for women who smoked for more than 5 years before their FFTP. These findings suggest that smoking during the prereproductive years may increase breast cancer risk for mutation carriers, warranting further investigation.

Disclosure of Potential Conflicts of Interest

D.G. Evans is a consultant for AstraZeneca. M. Friedlander reports receiving speakers bureau honoraria from AstraZeneca, MSD, Takeda, Lilly, and Novartis, and is a consultant/advisory board member for AbbVie. C.F. Singer reports receiving speakers bureau honoraria from Novartis and Amgen, and is a consultant/advisory board member for Roche. No potential conflicts of interest were disclosed by the other authors.

Disclaimer

The content of this manuscript does not necessarily reflect the views or policies of the National Cancer Institute or any of the collaborating centers in the BCFR, nor does mention of trade names, commercial products, or organizations imply endorsement by the U.S. government or the Breast Cancer Family Registry.

Authors' Contributions

Conception and design: M.B. Terry, A.C. Antoniou, K.-A. Phillips, C.F. Singer, H. Olsson, J.L. Hopper, R.L. Milne, D.F. Easton, F.E. Van Leeuwen, M.A. Rookus, N. Andrieu, D.E. Goldgar

Development of methodology: H. Li, A.C. Antoniou, M.B. Daly, J.L. Hopper, D.F. Easton, M.A. Rookus, N. Andrieu, D.E. Goldgar

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): M.B. Terry, A.C. Antoniou, K.-A. Phillips, K. Kast, C. Engel, C. Noguès, D. Stoppa-Lyonnet, C. Lasset, P. Berthet, V. Mari, O. Caron, D. Barrowdale, D. Frost, C. Brewer, D.G. Evans, L. Izatt, L. Side, L. Walker, M. Tischkowitz, M.T. Rogers, M.E. Porteous, H.E.J. Meijers-Heijboer, J.J.P. Gille, M.J. Blok, N. Hoogerbrugge, M.B. Daly, I.L. Andrulis, S.S. Buys, E.M. John, S.-A. McLachlan, M. Friedlander, Y.Y. Tan, A. Osorio, T. Caldes, A. Jakubowska, J. Simard, C.F. Singer, E. Olah, M. Navratilova, L. Foretova, A.-M. Gerdes, B. Arver, H. Olsson, R.K. Schmutzler, J.L. Hopper, R.L. Milne, D.F. Easton, M.A. Rookus

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): H. Li, M.B. Terry, D.G. Evans, S.-A. McLachlan, T. Caldes, C.F. Singer, R.L. Milne, F.E. Van Leeuwen, M.A. Rookus, N. Andrieu, D.E. Goldgar

Writing, review, and/or revision of the manuscript: H. Li, M.B. Terry, K.-A. Phillips, K. Kast, C. Engel, C. Noguès, D. Stoppa-Lyonnet, O. Caron, D. Barrowdale, D. Frost, D.G. Evans, L. Izatt, L. Walker, M. Tischkowitz, M.T. Rogers, H.E.J. Meijers-Heijboer, M.J. Blok, N. Hoogerbrugge, M.B. Daly, I.L. Andrulis, S.S. Buys, E.M. John, S.-A. McLachlan, M. Friedlander, Y.Y. Tan, A. Osorio, A. Jakubowska, J. Simard, C.F. Singer, E. Olah, L. Foretova, A.-M. Gerdes, H. Olsson, R.K. Schmutzler, J.L. Hopper, R.L. Milne, D.F. Easton, F.E. Van Leeuwen, M.A. Rookus, N. Andrieu, D.E. Goldgar

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): T.M. Mooij, C. Engel, D. Barrowdale, D. Frost, D.G. Evans, C.F. Singer, M.-J. Roos-Blom, J.L. Hopper

Study supervision: K.-A. Phillips, J.L. Hopper, N. Andrieu, D.E. Goldgar

Other (coordinator of the GENEPSO study): C. Noguès

Acknowledgments

The Breast Cancer Family Registry (BCFR), and authors Mary Beth Terry, Irene Andrulis, David Goldgar, Saundra Buys, Esther John, and Mary Daly, were supported by grant UM1CA164920 from the NCI. This work was partially supported by the Spanish Ministry of Economy and Competitiveness (MINECO) SAF2014-57680-R and the Spanish Research Network on Rare diseases (CIBERER). This work was supported by the Canadian Institutes of Health Research for the "CIHR Team in Familial Risks of Breast Cancer" program (grant no. CRN-87521) and the Ministry of Economic Development, Innovation and Export Trade (grant no. PSR-SIIRI-701). The DKFZ study was supported by the German Cancer Research Center (DKFZ). EMBRACE and D.F. Easton are supported by Cancer Research UK grants C1287/A10118 and C1287/A11990. D. Gareth Evans is supported by an NIHR grant to the Biomedical Research Centre, Manchester (IS-BRC-1215-20007). The Investigators at The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust are supported by an NIHR grant to the Biomedical Research Centre at The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust. A.C. Antoniou is funded by Cancer Research UK grants C12292/A20861 and C12292/A11174. The German Consortium of Hereditary Breast and Ovarian Cancer (GC-HBOC) is supported by the German Cancer Aid (grant no. 110837, to R.K. Schmutzler). This work was supported by LIFE – Leipzig Research Center for Civilization Diseases, Universität Leipzig. LIFE is funded by means of the European Union, by the European Regional Development Fund (ERDF), and by means of the Free State of Saxony within the framework of the excellence initiative. The national French cohort, GENEPSO, was supported by a grant from the Fondation de France and the Ligue Nationale Contre le Cancer and is being supported by a grant from INCa as part of the European program ERA-NET on Translational Cancer Research (TRANSCAN-JTC2012, no. 2014-008). Hospital Clinico San Carlos (HCSC) was supported by a grant RD12/0036/0006 and 15/00059 from ISCIII (Spain) and partially supported by European Regional Development FEDER funds. The HEBON study is supported by the Dutch Cancer Society grants NKI1998-1854, NKI2004-3088, NKI2007-3756, the Netherlands Organisation of Scientific Research grant NWO 91109024, the Pink Ribbon grants 110005 and 2014-187. WO76, the BBMRI grant NWO 184.021.007/CP46, and the Transcan grant JTC 2012 Cancer 12-054. The International Hereditary Cancer Centre (IHCC) was supported by grant PBZ_KBN_122/P05/2004 and The National Centre for Research and Development (NCBR) within the framework of the international ERA-NET TRANSAN JTC 2012 application no. Cancer 12-054 (contract no. ERA-NET-TRANSCAN/07/2014). This work was also supported by grants to kConFab and the kConFab Follow-Up Study from Cancer Australia (809195, 1100868), the Australian National Breast Cancer Foundation (IF 17), the National Health and Medical Research Council (454508, 288704, 145684), the NIH (1RO1CA159868), the Queensland Cancer Fund, the Cancer Councils of New South Wales, Victoria, Tasmania and South Australia, and the Cancer Foundation of Western Australia. K.-A. Phillips is an Australian National Breast Cancer Foundation fellow. L. Foretova was supported by MH CZ - DRO (MMCI, 00209805) and by MEYS - NPS I - LO1413 (to L. Foretova, M. Navratilova). E. Olah and The Hungarian Breast and Ovarian Cancer Study were supported by Hungarian Research Grants KTIA-OTKA CK-80745, NKFI OTKA K-112228, and the Norwegian EEA Financial Mechanism HU0115/NA/2008-3/ÖP-9. H. Olsson and Lund-BRCA collaborators are supported by the Swedish Cancer Society, Lund Hospital Funds, and European Research Council Advanced Grant ERC-2011-294576. Stockholm-BRCA collaborators are supported by the Swedish Cancer Society. BCFR wishes to thank members and participants in the Breast Cancer Family Registry from the New York, Northern California, Ontario, Philadelphia, and Utah sites for their contributions to the study. BCFR-Australia wish to acknowledge Maggie Angelakos, Judi Maskiell, Gillian Dite, and Helen Tsimiklis. CNIO thanks Alicia Barroso, Rosario Alonso, and Guillermo Pita for their assistance. We acknowledge the GENEPSO Centers (the Coordinating Center: Institut Paoli-Calmettes, Marseille, France: Catherine Noguès, Lilian Laborde, Pauline Pontois, Emanuelle Breysse, Margot Berline) and the Collaborating Centers (Institut Curie, Paris, France: Dominique Stoppa-Lyonnet, Marion Gauthier-Villars, Bruno Buecher, Chrystelle Colas; Institut Gustave Roussy, Villejuif, France: Olivier Caron; Hôpital René Huguenin/Institut Curie, Saint Cloud: Catherine Noguès, Emmanuelle Mouret-Fourme, Claire Saule, Chrystelle Colas; Centre Paul Strauss, Strasbourg, France: Jean-Pierre Fricker; Centre Léon Bérard, Lyon, France: Christine Lasset, Valérie Bonadona, Sophie Dussard; Centre François Baclesse, Caen, France: Pascaline Berthet; Hôpital d'Enfants CHU Dijon – Centre Georges François Leclerc, Dijon, France: Laurence Faivre; Centre Alexis Vautrin, Vandoeuvre-les-Nancy, France: Elisabeth Luporsi; Centre Antoine Lacassagne, Nice, France: Véronique Mari; Institut Claudius Regaud, Toulouse, France: Laurence Gladieff; Réseau Oncogénétique Poitou Charente, Niort: Paul Gesta, Stéphanie Chieze-Valéro; Institut Paoli-Calmettes, Marseille, France: Catherine Noguès, Jessica Moretta Hagay Sobol, François Eisinger, Cornel Popovici; Institut Bergonié, Bordeaux, France: Michel Longy; Centre Eugène Marquis, Rennes: Louise Grivelli; GH Pitié Salpétrière, Paris, France: Chrystelle Colas, Florent Soubrier, Patrick Benusiglio; CHU Arnaud de Villeneuve, Montpellier, France: Isabelle Coupier, Pascal Pujol, Carole Corsini; Centres Paul Papin/ICO, Angers: Marie-Emmanuelle Morin-Meschin; Clinique Catherine de Sienne, Nantes, France: Alain Lortholary; Centre Oscar Lambret, Lille, France: Claude Adenis, Audrey Maillez; Institut Jean Godinot, Reims, France: Tan Dat Nguyen; Centre René Gauducheau, Nantes, France: Capucine Delnatte, Caroline Abadie; Centre Henri Becquerel, Rouen, France: Julie Tinat, Isabelle Tennevet; Hôpital Civil, Strasbourg, France: Christine Maugard; Centre Jean Perrin, Clermont-Ferrand, France: Yves-Jean Bignon, Mathilde Gay Bellile; Polyclinique Courlancy, Reims, France: Clotilde Penet; Clinique Sainte Catherine, Avignon, France: Hélène Dreyfus; Hôpital Saint-Louis, Paris, France: Odile Cohen-Haguenauer; CHRU Dupuytren, Limoges, France: Brigitte Gilbert, Laurence Venat-Bouvet; CHU de Grenoble: Dominique Leroux, Clémentine Legrand, Hélène Dreyfus; Hôpital de la Timone, Marseille, France: Hélène Zattara-Cannoni; Hôpital Jacques Monod, le Havre, France: Valérie Layet, Elodie Lacaze; CHU Chambéry, Chambéry, France: Sandra Fert-Ferrer; Hôpital Clarac, Fort de France: Odile Bera; CHU la Milétrie, Poitiers, France: Brigitte Gilbert-Dussardier, David Tougeron, Stéphanie Chieze-Valéro; Hôpital Saint Louis, la Rochelle, France: Hakima Lallaoui; CH Pellegrin, Bordeaux, France: Julie Tinat). HCSC acknowledges Alicia Tosar and Paula Diaque for their technical assistance. The Hereditary Breast and Ovarian Cancer Research Group Netherlands (HEBON) consists of the following Collaborating Centers: Netherlands Cancer Institute (coordinating center), Amsterdam, the Netherlands: M.A. Rookus, F.B.L. Hogervorst, F.E. van Leeuwen, M.A. Adank, M.K. Schmidt, N.S. Russell, J.L. de Lange, R. Wijnands, D.J. Jenner; Erasmus Medical Center, Rotterdam, the Netherlands: J.M. Collée, A.M.W. van den Ouweland, M.J. Hooning, C. Seynaeve, C.H.M. van Deurzen, I.M. Obdeijn; Leiden University Medical Center, Leiden, the Netherlands: C.J. van Asperen, J.T. Wijnen, R.A.E.M. Tollenaar, P. Devilee, T.C.T.E.F. van Cronenburg; Radboud University Nijmegen Medical Center, Nijmegen, the Netherlands: C.M. Kets, A.R. Mensenkamp; University Medical Center Utrecht, Utrecht, the Netherlands: M.G.E.M. Ausems, R.B. van der Luijt, C.C. van der Pol; Amsterdam Medical Center, Amsterdam, the Netherlands: C.M. Aalfs, H.E.J. Meijers-Heijboer, T.A.M. van Os; VU University Medical Center, Amsterdam, the Netherlands: K. van Engelen, J.J.P. Gille, Q. Waisfisz; Maastricht University Medical Center, Maastricht, the Netherlands: E.B. Gómez-Garcia, M.J. Blok; University of Groningen, Groningen, the Netherlands: J.C. Oosterwijk, A.H. van der Hout, M.J. Mourits, G.H. de Bock; The Netherlands Comprehensive Cancer Organisation (IKNL): S. Siesling, J.Verloop; the nationwide network and registry of histo- and cytopathology in the Netherlands (PALGA): L.I.H. Overbeek. HEBON thanks the study participants and the registration teams of IKNL and PALGA for part of the data collection. INHERIT would like to thank Dr. Martine Dumont for sample management and skillful assistance. We thank Stephanie Nesci, Sandra Picken, Lucy Stanhope, Sarah O'Connor, Heather Thorne, Eveline Niedermayr, all the kConFab research nurses and staff, the heads and staff of the Australian and New Zealand Family Cancer Clinics, and the many families who contribute to kConFab for their contributions to this resource. MMCI, Brno, Czech Republic - many thanks to Dita Hanouskova, research nurse, Jitka Berkovcova, research technician, for data collection and management. We wish to thank the Hungarian Breast and Ovarian Cancer Study Group members (Maria Balogh, Janos Papp, Matrai Zoltan, Judit Franko Department of Molecular Genetics, National Institute of Oncology, Budapest, Hungary) and the clinicians and patients for their contributions to this study. Swedish scientists participating as SWE-BRCA collaborators are from Lund University and University Hospital (Lund, Sweden): Håkan Olsson, Carolina Ellberg; and from Stockholm and Karolinska University Hospital (Stockholm, Sweden): Brita Arver.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received May 15, 2019; revised August 8, 2019; accepted November 22, 2019; published first December 2, 2019.

Published OnlineFirst December 2, 2019; DOI: 10.1158/1055-9965.EPI-19-0546

References

1. Kuchenbaecker KB, Hopper JL, Barnes DR, Phillips KA, Mooij TM, Roos-Blom MJ, et al. Risks of breast, ovarian, and contralateral breast cancer for BRCA1 and BRCA2 mutation carriers. JAMA 2017;317:2402–16.
2. Hamajima N, Hirose K, Tajima K, Rohan T, Calle EE, Heath CW Jr, et al. Alcohol, tobacco and breast cancer–collaborative reanalysis of individual data from 53 epidemiological studies, including 58,515 women with breast cancer and 95,067 women without the disease. Br J Cancer 2002;87:1234–45.
3. Gaudet MM, Gapstur SM, Sun J, Diver WR, Hannan LM, Thun MJ. Active smoking and breast cancer risk: original cohort data and meta-analysis. J Natl Cancer Inst 2013;105:515–25.
4. Liu Y, Colditz GA, Rosner B, Berkey CS, Collins LC, Schnitt SJ, et al. Alcohol intake between menarche and first pregnancy: a prospective study of breast cancer risk. J Natl Cancer Inst 2013;105:1571–8.
5. Gaudet MM, Carter BD, Brinton LA, Falk RT, Gram IT, Luo J, et al. Pooled analysis of active cigarette smoking and invasive breast cancer risk in 14 cohort studies. Int J Epidemiol 2017;46:881–93.
6. McGuire V, John EM, Felberg A, Haile RW, Boyd NF, Thomas DC, et al. No increased risk of breast cancer associated with alcohol consumption among carriers of BRCA1 and BRCA2 mutations ages <50 years. Cancer Epidemiol Biomarkers Prev 2006;15:1565–7.
7. Moorman PG, Iversen ES, Marcom PK, Marks JR, Wang F, Kathleen Cuningham Consortium for Research into Familial Breast Cancer, et al. Evaluation of established breast cancer risk factors as modifiers of BRCA1 or BRCA2: a multi-center case-only analysis. Breast Cancer Res Treat 2010;124:441–51.
8. Breast Cancer Family Registry; Kathleen Cuningham Consortium for Research into Familial Breast Cancer (Australasia); Ontario Cancer Genetics Network (Canada). Smoking and risk of breast cancer in carriers of mutations in BRCA1 or BRCA2 aged less than 50 years. Breast Cancer Res Treat 2008;109:67–75.
9. Brunet JS, Ghadirian P, Rebbeck TR, Lerman C, Garber JE, Tonin PN, et al. Effect of smoking on breast cancer in carriers of mutant BRCA1 or BRCA2 genes. J Natl Cancer Inst 1998;90:761–6.
10. Colilla S, Kantoff PW, Neuhausen SL, Godwin AK, Daly MB, Narod SA, et al. The joint effect of smoking and AIB1 on breast cancer risk in BRCA1 mutation carriers. Carcinogenesis 2006;27:599–605.
11. Friebel TM, Domchek SM, Rebbeck TR. Modifiers of cancer risk in BRCA1 and BRCA2 mutation carriers: systematic review and meta-analysis. J Natl Cancer Inst 2014;106:dju091.
12. Ghadirian P, Lubinski J, Lynch H, Cybulski C, Lynch H, Neuhausen S, et al. Smoking and the risk of breast cancer among carriers of BRCA mutations. Int J Cancer 2004;110:413–6.
13. Ginsburg O, Ghadirian P, Lubinski J, Cybulski C, Lynch H, Neuhausen S, et al. Smoking and the risk of breast cancer in BRCA1 and BRCA2 carriers: an update. Breast Cancer Res Treat 2009;114:127–35.
14. Gronwald J, Byrski T, Huzarski T, Cybulski C, Sun P, Tulman A, et al. Influence of selected lifestyle factors on breast and ovarian cancer risk in BRCA1 mutation carriers from Poland. Breast Cancer Res Treat 2006;95:105–9.
15. Nkondjock A, Robidoux A, Paredes Y, Narod SA, Ghadirian P. Diet, lifestyle and BRCA-related breast cancer risk among French-Canadians. Breast Cancer Res Treat 2006;98:285–94.
16. Allen NE, Beral V, Casabonne D, Kan SW, Reeves GK, Brown A, et al. Moderate alcohol intake and cancer incidence in women. J Natl Cancer Inst 2009;101:296–305.
17. World Health Organization, International Agency for Research on Cancer. IARC Monographs on the evaluation of carcinogenic risks to humans. Allyl compounds, aldehydes, epoxides, and peroxides. Lyon, France: World Health Organization, International Agency for Research on Cancer; 1985. p. 36.
18. Tan SLW, Chadha S, Liu Y, Gabasova E, Perera D, Ahmed K, et al. A class of environmental and endogenous toxins induces BRCA2 haploinsufficiency and genome instability. Cell 2017;169:1105–18.
19. Goldgar D, Bonnardel C, Renard H, Yaqoubi O. The International BRCA1/2 carrier cohort study: purpose, rationale, and study design. Breast Cancer Res 2000;2:E010.
20. Thorne H, Mitchell G, Fox S. kConFab: a familial breast cancer consortium facilitating research and translational oncology. J Natl Cancer Inst Monogr 2011;2011:79–81.
21. Phillips KA, Butow PN, Stewart AE, Chang JH, Weideman PC, Price MA, et al. Predictors of participation in clinical and psychosocial follow-up of the kConFab breast cancer family cohort. Fam Cancer 2005;4:105–13.
22. John EM, Hopper JL, Beck JC, Knight JA, Neuhausen SL, Senie RT, et al. The Breast Cancer Family Registry: an infrastructure for cooperative multinational, interdisciplinary and translational studies of the genetic epidemiology of breast cancer. Breast Cancer Res 2004;6:R375–R89.
23. Terry MB, Phillips KA, Daly MB, John EM, Andrulis IL, Buys SS, et al. Cohort profile: the breast cancer prospective family study cohort (ProF-SC). Int J Epidemiol 2016;45:683–92.
24. Chen WY, Rosner B, Hankinson SE, Colditz GA, Willett WC. Moderate alcohol consumption during adult life, drinking patterns, and breast cancer risk. JAMA 2011;306:1884—90.
25. Terry MB, Zhang FF, Kabat G, Britton JA, Teitelbaum SL, Neugut AI, et al. Lifetime alcohol intake and breast cancer risk. Ann Epidemiol 2006;16:230–40.
26. Antoniou AC, Goldgar DE, Andrieu N, Chang-Claude J, Brohet R, Rookus MA, et al. A weighted cohort approach for analysing factors modifying disease risks in carriers of high-risk susceptibility genes. Genet Epidemiol 2005;29:1–11.
27. Feigelson HS, Calle EE, Robertson AS, Wingo PA, Thun MJ. Alcohol consumption increases the risk of fatal breast cancer (United States). Cancer Causes Control 2001;12:895–902.
28. Dennis J, Ghadirian P, Little J, Lubinski J, Gronwald J, Kim-Sing C, et al. Alcohol consumption and the risk of breast cancer among BRCA1 and BRCA2 mutation carriers. Breast 2010;19:479–83.
29. Seibold P, Vrieling A, Heinz J, Obi N, Sinn HP, Flesch-Janys D, et al. Pre-diagnostic smoking behaviour and poorer prognosis in a German breast cancer patient cohort - differential effects by tumour subtype, NAT2 status, BMI and alcohol intake. Cancer Epidemiol 2014;38:419–26.
30. Kwan ML, Chen WY, Flatt SW, Weltzien EK, Nechuta SJ, Poole EM, et al. Postdiagnosis alcohol consumption and breast cancer prognosis in the after breast cancer pooling project. Cancer Epidemiol Biomarkers Prev 2013;22:32–41.
31. Russo J, Russo IH.DNA labeling index and structure of the rat mammary gland as determinants of its susceptibility to carcinogenesis. J Natl Cancer Inst 1978;61:1451–9.
32. Russo J, Tay LK, Russo IH. Differentiation of the mammary gland and susceptibility to carcinogenesis. Breast Cancer Res Treat 1982;2:5–73.
33. Terry MB, Liao Y, Kast K, Antoniou AC, McDonald JA, Mooij TM, et al. The influence of number and timing of pregnancies on breast cancer risk for women with BRCA1 or BRCA2 mutations. JNCI Cancer Spectr 2018;2:pky078.

Cancer Epidemiology, Biomarkers & Prevention

AACR American Association for Cancer Research

Alcohol Consumption, Cigarette Smoking, and Risk of Breast Cancer for *BRCA1* and *BRCA2* Mutation Carriers: Results from The BRCA1 and BRCA2 Cohort Consortium

Hongyan Li, Mary Beth Terry, Antonis C. Antoniou, et al.

Cancer Epidemiol Biomarkers Prev 2020;29:368-378. Published OnlineFirst December 2, 2019.