Risks of Breast, Ovarian, and Contralateral Breast Cancer for BRCA1 and BRCA2 Mutation Carriers

Karoline B. Kuchenbaecker, Ph.D.¹,², John L. Hopper, Ph.D.³, Daniel R. Barnes, Ph.D.⁴, Kelly-Anne Phillips, M.D.³-⁶, Thea M. Mooij M.Sc.⁷, Marie-José Roos-Blom Ph.D.⁷, Sarah Jervis, Ph.D.¹ ⁹, D. Gareth Evans, M.D., Ph.D.¹⁰, Daniel Barrowdale, M.Sc¹, Debra Frost¹, Julian Adlard, M.D.¹¹, Kai-ren Ong, M.D.¹², Louise Izatt, M.D.¹³, Marc Tischkowitz, M.D., Ph.D.¹⁴, Ros Eeles, M.D., Ph.D.¹⁵, Rosemarie Davidson, M.D.¹⁶, Shirley Hodgson, M.D.¹⁷, Steve Ellis, M.Sc.¹, Catherine Nogues, M.D.¹⁸, Christine Lasset, M.D.¹⁹, Dominique Stoppa-Lyonnet, M.D., Ph.D.²⁰-²², Jean-Pierre Fricker, M.D.²³, Laurence Faivre, M.D., Ph.D.²⁴-²⁵, Pascaline Berthet, M.D.²⁶, Maartje J. Hooning, M.D., Ph.D.²⁷, Lizet E. van der Kolk, M.D., Ph.D.²⁸, Carolien M. Kets, M.D., Ph.D.²⁹, Muriel A. Adank, M.D., Ph.D.³⁰, Esther M. John, Ph.D.³¹, Wendy K. Chung, M.D., Ph.D.³², Irene L. Andruslis, Ph.D.³³,³⁴, Melissa Southey, Ph.D.³⁵, Mary B. Daly, M.D., Ph.D.³⁶, Saundra S. Buys, M.D.³⁷, Ana Osorio, Ph.D.³⁸,³⁹, Christoph Engel, M.D.⁴⁰,⁴¹, Karin Kast, M.D.⁴²,⁴³,⁴⁴, Rita K. Schmutzler, M.D., Ph.D.⁴⁵, Trinidad Caldes, M.D.⁴⁶, Anna Jakubowska, Ph.D.⁴⁷, Jacques Simard, Ph.D.⁴⁸, Michael L. Friedlander, M.D., Ph.D.⁴⁹,⁵⁰, Sue-Anne McLachlan, M.D.⁴,⁵¹, Eva Machackova, Ph.D.⁵², Lenka Foretova, M.D., Ph.D.⁵², Yen Y. Tan, Ph.D.⁵³,⁵⁴, Christian F. Singer, Ph.D.⁵⁵, Edith Olah, Ph.D.⁵⁶, Anne-Marie Gerdes, M.D., Ph.D.⁵⁷, Brita Arver, M.D., Ph.D.⁵⁸, Håkan Olsson, M.D., Ph.D.⁵⁹, Flora E. van Leeuwen, Ph.D.⁷, Roger L. Milne, Ph.D.⁵⁹, Nadine Andrieu, Ph.D.⁶⁰-⁶³, David E. Goldgar, Ph.D.⁶⁴, Mary Beth Terry, Ph.D.⁶⁵, Matti A. Rookus, Ph.D.⁺,_supp, Douglas F. Easton, Ph.D.⁺,¹, Antonis C. Antoniou, Ph.D.⁺,¹

Author affiliations

1. Centre for Cancer Genetic Epidemiology, Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK.
2. The Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, Hinxton, Cambridge, UK.
3. Centre for Epidemiology and Biostatistics, Melbourne School of Population Health, The University of Melbourne, Melbourne, Australia.

4. Division of Cancer Medicine, Peter MacCallum Cancer Centre, Melbourne, Australia.

5. Department of Medicine, St Vincent’s Hospital, The University of Melbourne, Parkville, Australia.

6. The Sir Peter MacCallum Department of Oncology University of Melbourne, Parkville, Australia.

7. Department of Epidemiology, Netherlands Cancer Institute, Amsterdam, The Netherlands.

8. Department of Medical Informatics, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands.

9. Mathematics Institute, University of Warwick, Coventry, UK.

10. Genomic Medicine, Manchester Academic Health Sciences Centre, Institute of Human Development, Manchester University, Central Manchester University Hospitals NHS Foundation Trust, Manchester, UK.

11. Yorkshire Regional Genetics Service, Chapel Allerton Hospital, Leeds, UK.

12. West Midlands Regional Genetics Service, Birmingham Women’s Hospital Healthcare NHS Trust, Edgbaston, Birmingham, UK.


14. Department of Medical Genetics and National Institute for Health Research Cambridge Biomedical Research Centre, University of Cambridge, Cambridge, UK.

15. Oncogenetics Team, The Institute of Cancer Research and Royal Marsden NHS Foundation Trust, Sutton, UK.

16. Department of Clinical Genetics, South Glasgow University Hospitals, Glasgow, UK.

17. Department of Clinical Genetics, St George’s, University of London, UK.

18. Oncogénétique Clinique, Hôpital René Huguenin/Institut Curie, Saint-Cloud, France.

19. Unité de Prévention et d’Epidémiologie Génétique, Centre Léon Bérard, Lyon, France.
1. Institut Curie, Department of Tumour Biology, Paris, France.

2. Institut Curie, INSERM U830, Paris, France.

3. Université Paris Descartes, Sorbonne Paris Cité, France.

4. Unité d’Oncogénétique, Centre Paul Strauss, Strasbourg, France.

5. Centre de Lutte Contre le Cancer Georges François Leclerc, Dijon, France.

6. Centre de Génétique, Hôpital d’Enfants, CHU Dijon, Dijon, France.

7. Centre François Baclesse, Caen, France.

8. Department of Medical Oncology, Family Cancer Clinic, Erasmus MC Cancer Institute, Rotterdam, The Netherlands.

9. Family Cancer Clinic, Netherlands Cancer Institute, Amsterdam, The Netherlands.

10. Department of Human Genetics, Radboud University Medical Center, Nijmegen, The Netherlands.

11. Department of Clinical Genetics, VU University Medical Center, Amsterdam, The Netherlands.

12. Department of Epidemiology, Cancer Prevention Institute of California, Fremont, CA USA.

13. Departments of Pedicatrics and Medicine, Columbia University, New York, NY, 10032 USA.

14. Department of Molecular Genetics, University of Toronto, Toronto, Ontario, Canada.

15. Lunenfeld-Tanenbaum Research Institute, Sinai Health System, Toronto, Ontario, Canada.

16. Genetic Epidemiology Laboratory, Department of Pathology, The University of Melbourne, Victoria, Australia.

17. Department of Clinical Genetics, Fox Chase Cancer Center, Philadelphia, PA, USA.

18. Department of Medicine, Huntsman Cancer Institute, Salt Lake City, UT, USA.

19. Human Genetics Group, Spanish National Cancer Centre (CNIO), Madrid, Spain.

20. Biomedical Network on Rare Diseases (CIBERER), Madrid, Spain.
40. Institute for Medical Informatics, Statistics and Epidemiology, University of Leipzig, Germany.
41. LIFE - Leipzig Research Centre for Civilization Diseases, University of Leipzig, Leipzig, Germany.
42. Department of Gynaecology and Obstetrics, University Hospital Carl Gustav Carus, Dresden, Germany.
43. National Center for Tumor Diseases (NCT), Partner Site Dresden, Germany.
44. German Cancer Consortium (DKTK), Dresden and German Cancer Research Center (DKFZ), Heidelberg, Germany.
45. Center for Familial Breast and Ovarian Cancer, Center for Integrated Oncology (CIO), Medical Faculty, University of Cologne and University Hospital Cologne, Germany.
46. Molecular Oncology Laboratory, Hospital Clinico San Carlos, IdISSC, Madrid, Spain.
47. Department of Genetics and Pathology, Pomeranian Medical University, Szczecin, Poland.
48. Genomics Center, Centre Hospitalier Universitaire de Québec Research Center and Laval University, Quebec City (Quebec), Canada.
49. Prince of Wales Clinical School, University of New South Wales, Sydney, Australia.
50. Department of Medical Oncology, Prince of Wales Hospital, Randwick, 2031, Australia
51. Department of Medical Oncology, St Vincent's Hospital, Fitzroy, Australia.
52. Department of Cancer Epidemiology and Genetics, Masaryk Memorial Cancer Institute, Brno, Czech Republic.
53. Department of Obstetrics and Gynecology and Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria.
54. QIMR Berghofer Medical Research Institute, 300 Herston Rd, Herston QLD 4006, Australia.
55. Department of Molecular Genetics, National Institute of Oncology, Budapest, Hungary.
56. Department of Clinical Genetics, Copenhagen University Hospital Rigshospitaal, Copenhagen, Denmark.

57. The Department of Oncology and Pathology, Karolinska Institute, Stockholm, Sweden.

58. Department of Oncology, Lund University Hospital, Lund, Sweden.

59. Cancer Epidemiology Centre, Cancer Council Victoria, Melbourne, Australia.

60. Inserm U900, Paris, France.

61. Institut Curie, Paris, France.


63. PSL Research University, Paris, France.

64. Department of Dermatology, University of Utah School of Medicine, Salt Lake City, UT, USA.

65. Department of Epidemiology, Columbia University, New York, NY, USA.

# Joint first authors

* Joint senior authors

**Correspondence:**

Antonis C. Antoniou

Strangeways Research Laboratory

Department of Public Health and Primary Care

University of Cambridge

Worts Causeway

Cambridge CB1 8RN

U.K.

Email: aca20@medschl.cam.ac.uk

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Key Points

Question: What are the breast and ovarian cancer risks for BRCA1 and BRCA2 mutation carriers and are they related to family history of cancer and mutation position?

Findings: In a prospective cohort of 9,856 mutation carriers, mainly ascertained through cancer genetic clinics, the cumulative breast cancer risk to age 80 years was 72% for BRCA1 and 69% for BRCA2 carriers. The cumulative ovarian cancer risk to age 80 was 44% for BRCA1 and 17% for BRCA2 carriers. Cancer risks differed by cancer family history and mutation position.

Meaning: These findings provide cancer risk patterns based on BRCA status using prospective data. Family history and mutation position are important additional variables in risk assessment.
Abstract

Importance: The clinical management of BRCA1 and BRCA2 mutation carriers requires accurate, prospective cancer risk estimates.

Objectives: To estimate age-specific risks of breast cancer, ovarian cancer, and contralateral breast cancer for mutation carriers and to evaluate risk modification by family cancer history and mutation location.

Design and setting: Prospective cohort study of BRCA1 and BRCA2 female carriers recruited from 1997-2011 through the International BRCA1/2 Carrier Cohort Study, the Breast Cancer Family Registry and the Kathleen Cuningham Foundation Consortium for Research into Familial Breast Cancer, with ascertainment through family clinics (94%) and population-based studies (6%). The majority were from large national studies in the UK (EMBRACE), the Netherlands (HEBON) and France (GENEPSEO). The follow-up ended December 2013.

Participants: 6,036 BRCA1 and 3,820 BRCA2 mutation carriers at baseline (5,046 unaffected, 4,810 with breast or ovarian cancer or both at baseline; median follow-up: 5 years).

Exposures: BRCA1/2 mutations, family cancer history, mutation location.

Main Outcomes and Measures: Annual incidences, standardized incidence ratios, and cumulative risks of breast, ovarian and contralateral breast cancer.

Results: Among 3,886 women (median age 38, IQR 30-46) eligible for the breast cancer analysis, 5,066 women (median age 38, IQR 31-47) eligible for the ovarian cancer analysis, and 2,213 women (median age 47, IQR 40-55) eligible for the contralateral breast cancer analysis, 426 were diagnosed with breast cancer, 109 with ovarian cancer, and 245 with contralateral breast cancer, respectively, during follow-up. The cumulative breast cancer risk to age 80 years was 72% (95%CI:65-79%) for BRCA1 and 69% (95%CI:61-77%) for BRCA2
carriers. The breast cancer incidences increased rapidly in early adulthood, until ages 30-40
for BRCA1 and until ages 40-50 for BRCA2 carriers, then remained at a similar, constant
incidence (20-30 per 1,000 person-years) until age 80. The cumulative ovarian cancer risk
to age 80 years was 44% (95%CI:36-53%) for BRCA1 and 17% (95%CI:11-25%) for BRCA2
carriers. For contralateral breast cancer, the cumulative risk 20 years after breast cancer
diagnosis was 40% (95%CI:35-45%) for BRCA1 and 26% (95%CI:20-33%) for BRCA2
carriers (Hazard Ratio (HR) for comparing BRCA2 vs BRCA1 0.62, 95%CI:0.47-0.82, P-
diff=0.001). Breast cancer risk increased with increasing number of first- and second-degree
relatives diagnosed with breast cancer for both BRCA1 (P-trend<0.001, HR for ≥2 vs no
affected relatives 1.99(95%CI:1.41-2.82)) and BRCA2 carriers (P-trend=0.02, HR=1.91
(95%CI:1.08-3.37)). Breast cancer risk was higher if mutations were located outside vs
within the regions bounded by positions c.2282-c.4071 in BRCA1 (HR=1.46 (95%CI:1.11-
1.93), p=0.007) and c.2831-c.6401 in BRCA2 (HR=1.93 (95%CI:1.36-2.74), p<0.001).

Conclusions and Relevance: These findings provide patterns of cancer risk based on
BRCA status using prospective data collection, and demonstrate the potential importance of
family history and mutation location in risk assessment.
Introduction

The optimal clinical management of women with BRCA1 and BRCA2 mutations depends on accurate age-specific cancer risk estimates. These can be used to estimate the absolute risk-reduction from preventive strategies and to inform decisions about the age to commence cancer screening.\(^1\)

Based on retrospective studies\(^2\text{-}^{11}\) the cumulative breast cancer risk estimates to age 70 years range from 40 to 87\% for BRCA1 and 27 to 84\% for BRCA2 carriers. The corresponding ovarian cancer risks vary from 16 to 68\% for BRCA1 and 11 to 30\% for BRCA2 carriers. In these studies, risk estimates have wide confidence intervals. Differences in sampling (population-based/high-risk families), population- and mutation-characteristics, analytic methods, and other genetic- and lifestyle/hormonal-factors, are possible explanations for the variation in risk estimates.\(^12\)

Since BRCA1 and BRCA2 mutations are rare in the population, most retrospective penetrance estimates have been derived from family-based studies. Typically, mutation screening has been of affected women, selected on the basis of young age at diagnosis, or cancer family history. Cancer risks are then estimated using the known or inferred genotypes of the relatives. Estimates from such retrospective, family-based studies are prone to bias if analyses are not correctly adjusted for the ascertainment process, or if there are inaccuracies in family history.

Prospective cohort studies, in which mutation carriers are recruited on the basis of their mutation status and followed over time, may avoid these issues. Since the precision of risk estimates depends on the number of prospective-incident cancers, a very large sample with...
long follow-up is required. Prospective penetrance estimates have been based on small
samples (<64 breast, 31 ovarian cancers) and are imprecise\textsuperscript{13-15}. The purpose of this study
was to estimate age-specific risks of breast, ovarian, and contralateral breast cancer using
data from a large prospective cohort.

Methods

Participants
We used prospective cohort data on carriers of pathogenic BRCA1 and BRCA2 mutation
carriers recruited through three consortia, the International BRCA1/2 Carrier Cohort Study
(IBCCS), the Breast Cancer Family Registry (BCFR), and the Kathleen Cuningham
Foundation Consortium for Research Into Familial Breast Cancer (kConFab, details in
Supplementary Material). All centres in these consortia obtained written informed consent
from study participants and local ethical review committees approved protocols.

Briefly, for IBCCS, data were available from 7666 female carriers recruited between 1997
and 2011 from 18 European cancer genetics centres and Quebec province, Canada. The
majority were from large national studies in the UK, the Netherlands and France. All centres
conducted active follow-up through follow-up questionnaires. In addition to the active follow-
up in all studies, passive follow-up through linkage with cancer, pathology and death
registries was obtained in countries where this is available (cancer/death registries in
Denmark, The Netherlands, Sweden and the UK; pathology registries to collect information
on preventive surgeries in Denmark and The Netherlands) together with medical record
validation of self-reported cancer diagnoses and preventive surgeries.
BCFR is a family cohort that includes data on 1,570 mutation carriers recruited from six sites in Australia, Canada, and the U.S.A. Families were followed up regularly, through annual approaches to probands and 5-year systematic follow-up of families collecting epidemiological and demographic data from all participants. kConFab included 620 mutation carriers from multiple-case families ascertained through family cancer clinics in Australia and New Zealand since 1997. Participants were systematically followed-up using a mailed follow-up questionnaire administered every 3 years. The end of follow-up was December 2013.

**Eligibility and censoring**

For each of the three analyses (breast cancer risk, contralateral breast cancer risk and ovarian cancer risk) we defined a different group eligible at baseline (Figure 1). Baseline was defined to be the age at study recruitment or age at the genetic test, whichever was last.

**Breast cancer risk**

Women were included in the estimation of first breast cancer risk if, at completion of the baseline questionnaire, they had not been diagnosed with any cancer (excluding non-melanoma skin cancer) nor undergone risk-reducing bilateral mastectomy (with mastectomy: n=304 BRCA1; n=148 BRCA2, Supplementary Methods). Women were followed from baseline until the first of: attained age 80 years; death; completion of last follow-up questionnaire, or last record linkage (if conducted), whichever came last; risk reducing bilateral mastectomy; or diagnosis of any first cancer (excluding non-melanoma skin cancer). Women diagnosed with breast cancer (invasive or non-invasive (DCIS)) during follow-up were considered as affected. Since information on cancers was partly self-reported, tumor phenotype specific data were not available other than invasiveness. Therefore, all types of
breast cancer were included in the analysis. Additional analyses were performed in which: (i) affected women were considered to be only those diagnosed with invasive disease; and (ii) women were censored at the age of risk-reducing salpingo-oophorectomy (Supplementary Methods).

Ovarian cancer risk

Women were included in the ovarian cancer analysis if at baseline they had not been diagnosed with ovarian cancer nor undergone risk-reducing salpingo-oophorectomy (with oophorectomy: n=1,808 BRCA1; and n=969 BRCA2). Women with a history of breast or non-melanoma skin cancer were included in the analysis but women with other cancers were not. Women were followed from baseline until the first of: attained age 80 years; death; completion of last follow-up questionnaire or last record linkage (whichever came last); risk-reducing salpingo-oophorectomy (or salpingectomy or removal of ovaries for other reasons); any cancer diagnosis (excluding breast and non-melanoma skin cancer). Only women diagnosed with invasive ovarian (or fallopian tube or peritoneal) cancer during follow-up were considered affected.

Contralateral breast cancer risk

Women were included in the contralateral breast cancer analysis if they were diagnosed with a first breast cancer before the date of their last follow-up questionnaire (or record linkage) and had not been diagnosed with any other cancer (including contralateral breast cancer) nor undergone risk-reducing bilateral mastectomy before study entry. Only asynchronous contralateral breast cancer was considered, for which there had to be an interval of at least one year between first and second breast cancers. Eligible women entered follow-up at their baseline questionnaire date or one year after their first breast cancer diagnosis date (whichever later) and were followed until the first of: age 80 years; death; date at last follow-up; risk-reducing bilateral mastectomy or any cancer. Women diagnosed with asynchronous contralateral breast cancer during follow-up were assumed to be affected.
**Statistical Analysis**

Annual incidences of breast, ovarian and contralateral breast cancer per 1,000 person-years (PY) were estimated for 10-year age intervals using standard cohort analysis. Kaplan-Meier (KM) analysis was used to estimate cumulative risks. Standardized incidence ratios (SIRs) for breast and ovarian cancer, relative to population specific incidences, were also estimated (Supplementary Material).

We used Cox-regression to compare cancer risks for *BRCA1* mutation carriers with risks for *BRCA2* carriers over all age groups and by attained age. To test for heterogeneity by country, we carried out Cox-regression based on a chi-square (n-1) degree of freedom test, where n=6, is the number of countries, on the estimated hazard ratios for each country compared to the baseline country (UK). The contralateral breast cancer analysis was stratified by age at first breast cancer (before 40, between 40 and 49, 50 or older) and Cox-regression was used to compare risks between age-groups. We evaluated cancer risks by extent of self-reported family history of breast or ovarian cancer separately (Supplementary Methods). Women were classified by the number of cancers in first- or second-degree relatives (none, one, two or more). Separate categories for women with cancers of unknown type among relatives, and for those with unknown family history (“missing”) were defined and separate hazard ratios were estimated for these categories. A test for trend was performed using Cox-regression by including a continuous variable in the model representing the number of breast or ovarian cancers in female first- or second- degree relatives (taking values 0, 1, 2, 3, etc). Separate variables were derived for the number of breast and number of ovarian cancers in relatives. We also evaluated differences in breast and ovarian cancer by mutation position (based on base-pair location) using Cox regression. Mutations were grouped into regions based on differences in breast and ovarian cancer risks previously reported in retrospective studies\(^ {16-18}\). Mutations in *BRCA1* were grouped into 3 regions (5’ to
c.2281; c.2282 to c.4071; c.4072 to 3’). For \textit{BRCA2}, mutations were grouped in 3 regions using both the narrow and wide definitions of the “Ovarian Cancer Cluster Region”\textsuperscript{16} (wide: 5’ to c.2830, c.2831 to c.6401, c.6402 to 3’; narrow: 5’ to c.3846, c.3847 to c.6275, c.6276 to 3’, Supplementary Methods). For all analyses a robust variance approach, which clustered observations on family membership was used to adjust standard errors for the fact that the cohort included multiple women from the same family\textsuperscript{19}. Analyses were stratified by country (categories: UK, France, Netherlands, Australia, USA, other) and birth cohort (groups: before 1940, 1940-1949, 1950-1959, 1960-1969, 1970-1979, 1980 or later). Proportionality was evaluated using Schoenfeld residuals which was met for all analyses. Analyses were carried out in Stata(v.13). Statistical tests were considered significant based on 2-sided hypothesis tests with $P < .05$.

**Results**

A total of 9,856 patients, including 6,036 \textit{BRCA1} and 3,820 \textit{BRCA2} mutation carriers were available at baseline. The majority of women were ascertained through family clinics (94%) and the remainder (6%) were recruited from studies that used population-based ascertainment. Figure 1 and eTable1 summarize the baseline cohort study sample (N=9,856) and the assembly of the eligible prospective cohorts for each analysis. Table 1 summarizes the characteristics of the eligible women included in the prospective analyses. Information on follow-up completeness is summarized in eTable2. All studies conducted active follow-up with follow-up questionnaires, but the mean interval between questionnaires varied across studies (1.6 to 8.7 years, eTable2). In addition, in countries with registry information, active follow-up was complemented with passive follow-up through record linkage. On average, 7% of women in the cohort were lost to follow-up but this varied among studies (0 to 13%, eTable 2).
The breast cancer analysis was based on 3,886 eligible BRCA1 and BRCA2 mutation carriers (median age at study entry: 38 (interquartile range (IQR):30-46)) The ovarian cancer analysis was based on data from 5,066 women (median age at study entry: 38 (IQR=31-47)) and the contralateral breast cancer analysis was based on 2213 women (median age at start of follow-up: 47 (IQR=40-55)). During follow-up, among the eligible women, 426 were diagnosed with breast cancer (483 censored for risk-reducing bilateral mastectomy), 109 were diagnosed with ovarian cancer (1508 censored for risk-reducing salpingo-oophorectomy) and 245 were diagnosed with asynchronous contralateral breast cancer. The age-specific cancer incidences, SIRs and cumulative risks are shown in Table 2.

Breast cancer risks

For BRCA1 carriers, the breast cancer incidences per decade of age increased from 21-30 to 31-40 years of age, but then remained at 23.5-28.3 per 1000 person-years for ages 31-70 (P-trend=0.97). The peak incidence occurred in the 41-50 age group (28.3 per 1000 person-years, 95% confidence interval (CI):23.1-34.7). A similar pattern was seen for BRCA2 carriers, with peak incidence in the 51-60 age-group (30.6 per 1000 person-years, 95%CI:22.8-41.1) and incidence of 21.9-30.6 per 1000 person-years across ages 41-80 (P-trend=0.57). The estimated SIRs decreased with increasing age in both BRCA1 (P-trend<0.001) and BRCA2 carriers (P-trend<.001). The cumulative risk of breast cancer by age 80 was 72% (95%CI:65-79%) for BRCA1 and 69% (95%CI:61-77%) for BRCA2 carriers (Figure 2). While the cumulative risks for BRCA1 and BRCA2 carriers to age 80 years were similar, the cumulative risks to age 50 were higher for BRCA1 carriers (P=0.03).

The cumulative risk estimates for breast cancer by age 80 years when censoring at risk-reducing salpingo-oophorectomy were 70% (95%CI:60-80%) for BRCA1 and 75% (95%CI:67-83%) for BRCA2 carriers (Supplement, eTable 3, eFigure 1). From an analysis that excluded the known in-situ breast cancers, the corresponding risk-estimates were 68%
(95%CI:60-76%) for BRCA1 and 63% (95%CI:54-72%) for BRCA2 carriers (Supplement, eTable 4).

There were no significant differences in the estimated breast cancer incidences by country for either BRCA1 (P-heterogeneity=0.32) or BRCA2 carriers (P-heterogeneity=0.43, Supplement, eTable 5, eFigure 2). The estimated breast cancer risks were similar when analyses were carried out separately for women identified through family clinics and women who were relatives of mutation carriers identified through population-wide screening of breast cancer cases (eTable 6).

Ovarian cancer risks

There was an increase in ovarian cancer incidence with age up to 61-70 years for both BRCA1 and BRCA2 carriers. The incidences were higher for BRCA1 carriers (HR comparing BRCA1 versus BRCA2 = 3.6, 95%CI:2.2-5.9 P<.001). The SIRs did not vary with age for either gene (overall SIR 49.6 (95%CI:40.0-61.5), P-trend=0.86 for BRCA1; 13.7 (95%CI:9.1-20.7) P-trend=0.23 for BRCA2). The ovarian cancer cumulative risk to age 80 years was 44% (95%CI: 36-53%) for BRCA1 and 17% for BRCA2 carriers (95%CI:11-25%) (Table 2, Figure 2).

Contralateral breast cancer risks

The estimated incidence of contralateral breast cancer for BRCA1 carriers varied between 23 to 28 per 1000 person-years for the period up to 20 years after the first breast cancer diagnosis (Table 3; Supplement eTable 7). The cumulative risk of contralateral breast cancer at 20 years after the first breast cancer diagnosis was 40% (95%CI:35-45%). The HR for contralateral breast cancer declined with increasing age of the first breast (HR for women
diagnosed with the first breast cancer in ages 40-50 and >50 years was 0.81 (95%CI:0.58-1.12) and 0.71 (95%CI:0.45-1.11) respectively, relative to women diagnosed under age 40).

For BRCA2 carriers, the estimated contralateral breast cancer incidence varied between 13 to 18 per 1000 person years during the years after the first breast cancer diagnosis. The cumulative risk of contralateral breast cancer at 20 years after the first breast cancer diagnosis was 26% (95%CI:20-33%), and was lower than for BRCA1 carriers (HR comparing BRCA2 vs BRCA1 = 0.62, 95%CI: 0.47-0.82, P=0.001). The HR for contralateral breast cancer when first breast cancer diagnosis was when aged 40-50 was 0.73 (95%CI: 0.41-1.26) and 0.76 (95%CI:0.43-1.36) when the first breast cancer diagnosis was >50 years, compared to a first breast cancer under age 40.

When women were censored at the age of risk-reducing salpingo-oophorectomy, the contralateral breast cancer risks at 20 years after the first breast cancer were 38% (95%CI:31-45%) for BRCA1 and 34% (95%CI:25-45%) for BRCA2 carriers (Supplement, eTable 8).

To investigate potential survival bias, the analysis was repeated after excluding women whose first breast cancer diagnosis occurred >5 years prior to study recruitment. The estimated cumulative risk of contralateral breast cancer at 20 years after the first breast cancer diagnosis was 41% (95%CI:32-53%) for BRCA1 and 21% (95%CI:15-50%) for BRCA2 carriers.

Breast and ovarian cancer risks by family history

The estimated cumulative breast and ovarian cancer risks by family history are shown in Table 4 and eFigure 3. Breast cancer risk estimates for both BRCA1 and BRCA2 carriers increased with the number of first- and second-degree relatives diagnosed with breast cancer (p-trend:<.001 for BRCA1; 0.02 for BRCA2, Table 4). The breast cancer HR estimate
for women with two or more first- or second-degree relatives diagnosed with breast cancer compared with those with no family history of breast cancer was 1.99 (95%CI:1.41-2.82) for
BRCA1 (cumulative risk estimates to age 70 : 73% (95%CI: 65-80%) vs 53% (95%CI:39-69%)) and 1.91 (95%CI:1.08-3.37) for BRCA2 carriers (cumulative risks to age 70: 65% (95%CI: 56-74%) vs 39% (95%CI: 25-56%), Table 4).

There was no significant difference in ovarian cancer risk for BRCA1 carriers with family history of ovarian cancer compared with those without, (HR=1.37, 95%CI:0.89-2.11, Table 4; Supplement eFigure 3). A similar pattern was observed for BRCA2 carriers but the number of events for women with ovarian cancer family history was small (N=5). Results were similar when we restricted family history of cancer to first-degree relatives (Supplement eTable 9), or when analyses were stratified by the presence of family history of the second cancer (Supplement eTables 10, 11, 12 and 13 results in Supplementary Material). For BRCA1 mutation carriers, the risk of breast cancer was lower for women with a family history of ovarian cancer compared with those with no family history of ovarian cancer (HR=0.71, 95%CI:0.51-0.99 and HR=0.38, 95%CI:0.21-0.70 from analysis of women with a family history of breast cancer and from analysis of those without, respectively, Supplement eTable 12).

Breast and ovarian cancer risks by mutation position
BRCA1 mutations located outside the region bounded by positions c.2282 to c.4071 were associated with a significantly higher breast cancer risk compared to mutations within the region (HR=1.46 (95%CI:1.11-1.93), p=0.007, Table 4, eFigure 4) but there was no significant difference in ovarian cancer risk. There was no significant difference in the breast or ovarian cancer risks for either the BRCA1 c.68_69delAG or c.5266dupC mutations when compared to BRCA1 mutations in the same region (Table 4). BRCA2 mutations outside the OCCR region were associated with a significantly higher breast cancer risk compared to mutations within OCCR (based on the narrow OCCR definition: HR=1.70 (95%CI:1.18-2.46),
p=.005; based on the broad OCCR definition: HR=1.93 (95%CI:1.36-2.74), p<.001 Table 4)

but there was no significant difference in ovarian cancer risk. There was no significant
difference in breast cancer risk for BRCA2 c.5946delT mutation carriers compared to other
OCCR BRCA2 mutations (HR=0.73 95%CI:0.35-1.54, p=.41). The associations by mutation
position remained significant after adjusting for family history of breast cancer and after
excluding carriers of BRCA2: c.5946delT from the OCCR region (eTable14).

Discussion

This study estimated age-specific risks of breast, ovarian, and contralateral breast cancer for
BRCA1 and BRCA2 mutation carriers using data from a prospective cohort. Because the
study mainly included unaffected women identified by mutation screening based on cancer
family history, early age at onset of a family member, or both, the overall estimates are
relevant to mutation carriers identified through clinical testing. However, the wide range of
family histories represented allowed an examination of the relationship between family
history and cancer risk. The results indicate that family history is a strong risk factor for
mutation carriers and that cancer risks vary by mutation location, suggesting that
individualized counseling should incorporate both family history profiles and mutation
location.

The cumulative risk of developing breast cancer by age 80 was 72% for BRCA1 and 69% for
BRCA2 mutation carriers respectively. For ovarian cancer the cumulative risks by age 80
were 44% for BRCA1 and 17% for BRCA2 carriers. Breast cancer incidence for carriers
increased rapidly with age in early adulthood then plateaued to remain relatively constant
throughout the remaining lifetime. The age at which this plateau was reached was 31-40
years for BRCA1 carriers and 5-10 years later for BRCA2 carriers. The incidence during the
plateau was similar for both groups of mutation carriers. This is consistent with the model for
genetic risk of breast cancer based on twin data20, in which the age-specific incidence for
genetically susceptible women increases to a high constant level by a predetermined age that varies between families.

The estimated breast and ovarian cancer risks were consistent with findings from retrospective family-based studies. The breast cancer SIRs decreased with increasing age for both BRCA1 and BRCA2 carriers, but the estimates were higher than those previously reported for younger age groups. From this prospective study, the estimated cumulative risks of ovarian cancer were low to age 40 for BRCA1 mutation carriers, and to age 50 for BRCA2 mutation carriers.

This study was limited in the extent to which differences by birth cohort could be assessed because birth cohort was strongly associated with age. For age intervals with sufficient observations, there was no evidence of risk differences (Supplement, eFigure 5).

In line with retrospective studies of contralateral breast cancer risks, the present prospective analysis of BRCA1 and BRCA2 carriers combined demonstrated a higher risk when the first breast cancer was diagnosed before age 40 years versus after age 50 years (p=0.03).

The contralateral breast cancer analysis also included women diagnosed with breast cancer prior to study recruitment. The median interval between first breast cancer diagnosis and study recruitment was 4 years and this did not vary by the age at first breast cancer diagnosis or by gene. The inclusion of survivors could potentially bias the estimation of contralateral breast cancer risks, if such risks were related to the outcome of the first cancer; however, there is no strong evidence of such a relationship in the general population. Furthermore, the results were similar after excluding women whose first breast cancer diagnosis occurred >5 years prior to study recruitment, suggesting that any bias is likely to
be small. Contralateral breast cancer risks have been shown to be reduced by adjuvant treatment of the first cancer\textsuperscript{25,26}. \textit{BRCA2} carriers are more likely to develop estrogen-receptor positive cancers, so their lower contralateral breast cancer risk estimates may in part be due to greater use of endocrine therapy. Hormonal and chemotherapeutic treatments were not considered so the present estimates represent risks averaged over different treatments.

There was increasing breast cancer risk for both \textit{BRCA1} and \textit{BRCA2} carriers with increasing number of relatives who had been diagnosed with breast cancer. Similar patterns were observed for the risk of ovarian cancer but the number of events for women with family history of ovarian cancer was small. The overall breast cancer risk estimates were somewhat higher than those estimated by kin-cohort analyses, in which the risks are derived from cohorts of relatives of carriers identified among unselected cases\textsuperscript{3,22}. The present cohort of mutation carriers was primarily identified through clinical genetics centers and included women who, on average, are likely to have stronger family history of cancer compared with mutation carriers identified through population-based sampling of cases. Therefore, a likely explanation for the higher estimated risks in the present study is that cancer risks for mutation carriers are modified by genetic and non-genetic risk factors which aggregate in families, in line with evidence that other genetic factors modify cancer risks for mutation carriers\textsuperscript{18,27-30}. These results confirm that family history should be taken into account in determining cancer risks for carriers, as modelled explicitly in BOADICEA\textsuperscript{3}.

This prospective analysis validates retrospective analyses demonstrating that cancer risk varies by mutation location within the \textit{BRCA1} or \textit{BRCA2} gene\textsuperscript{16-18}. Consistent with those findings, mutations that lie in exon 11 of either gene were associated with a lower breast cancer risk and possibly higher ovarian cancer risk. The number of women in this prospective cohort was too small to estimate risks for additional, recently identified, breast or ovarian cancer cluster regions\textsuperscript{18}.
This study has several limitations. Data on tumor-phenotypes of cancers were not available. Therefore, the results represent average estimates over all phenotypes of breast and ovarian cancer. Although there was variation in the cancer risks for mutation carriers by cancer family history, the study sample was not identified through population screening of unaffected women. Therefore, the overall estimates may not be directly applicable to such women. The present results suggest that cancer risks for women with no family history are likely to be lower than those estimated here. The cancer risk estimates may be subject to some selection bias if the decision to participate in the study or opt for testing was related to factors that are associated with disease risk. It was not possible to contrast the unaffected study participants to all other unaffected family members who tested negative or who did not opt for a genetic test or for study participation, as those data could be not be collected. However, the analysis by family history addresses possible selection bias with respect to family history of cancer and the family history-specific estimates are expected to be unbiased. The number of events in some of the subgroups considered was small and therefore the estimates have wide confidence intervals. Family size was not taken into consideration because data on unaffected family members were not collected systematically. In addition, risk estimates are limited by the lack of information about the use of hormonal therapies to prevent either first primary or contralateral breast cancers.

Conclusions

These findings provide information on cancer risk for BRCA1 and BRCA2 mutation carriers using prospective data, and demonstrate the potential importance of family history and mutation location in risk assessment.
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Figure legends

- **Figure 1**: Assembly of analysis cohorts.

- **Figure 2**: Estimated cumulative risks of breast and ovarian cancer in mutation carriers. Kaplan-Meier estimates of cumulative risks of breast (A) and ovarian (B) cancer. In the breast cancer analysis, women were censored at risk-reducing bilateral mastectomy. In the ovarian cancer analysis women were censored for risk-reducing salpingo-oophorectomy. Number at risk indicates the number of women that remain at risk at the end of the 10-year age category (e.g. in panel A, there were 138 women with BRCA1 mutations still at risk of breast cancer at the end of the 50-60 years period). The earliest follow-up starts at age 18 years.

- **eFigure 1**: Estimated cumulative risk of breast cancer in mutation carriers with censoring at oophorectomy. Kaplan-Meier estimates of cumulative risks after censoring for risk-reducing salpingo-oophorectomy (RRSO). For comparison purposes the curves without censoring are also included. a) BRCA1 carriers and b) BRCA2 carriers. Number at risk indicates the number of women that remain at risk at the end of the 10-year age category. The earliest follow-up starts at age 18 years.

- **eFigure 2**: Study-specific breast and ovarian cancer standardised incidence rate estimates (with associated 95% confidence intervals). The y-axis (SIRs) is plotted on natural logarithmic scale. The number of mutation carriers by study contributing to the analysis are shown in eTable 5. Age and calendar-period specific population disease incidences were obtained from Cancer in Five Continents (http://ci5.iarc.fr/Default.aspx) and NORDCAN (http://www-dep.iarc.fr/NORDCAN/english/frame.asp).

- **eFigure 3**: Estimated cumulative risks of breast and ovarian cancer in mutation carriers, by breast and ovarian cancer family history (FH). Kaplan-Meier estimates of cumulative risks of breast cancer (BC) in A) BRCA1 carriers and B) BRCA2 carriers and risks of ovarian cancer (OC) in C) BRCA1 carriers and D)
BRCA2 carriers. Family history (FH) groupings: No family history of the respective cancer amongst 1st and 2nd degree relatives, one affected relative, or two or more relatives. “D” compares only any versus no family history due to limited observations. Number at risk indicates the number of women that remain at risk at the end of the 10-year age category. The earliest follow-up starts at age 18 years.

- **eFigure 4: Estimated cumulative risks of breast and ovarian cancer in mutation carriers, by mutation location.** Kaplan-Meier estimates of cumulative risks of breast cancer in A) BRCA1 carriers and B) BRCA2 carriers; and risks of ovarian cancer in C) BRCA1 carriers and D) BRCA2 carriers. Number at risk indicates the number of women that remain at risk at the end of the 10-year age category. The earliest follow-up starts at age 18 years.

- **eFigure 5: Age-specific breast cancer incidence estimates (with associated 95% confidence intervals) by year of birth (breast cancer analysis cohort).** (a) BRCA1 mutation carriers; (b) BRCA2 mutation carriers. Numbers in the graphs indicate the number of women contributing to the estimation.
Table captions

Table 1: Numbers of mutation carriers and incident cancers per study-group eligible for each of the analyses and other summary statistics.

Table 2: Breast and ovarian cancer incidence rates per 1000 person-years, Kaplan-Meier estimates of the cumulative risks and standardised incidence rates (SIR) by 10-year age groups.

Table 3: Contralateral breast cancer incidence rates per 1000 person-years and Kaplan Meier estimates of the cumulative risks of contralateral breast cancer, by time since first breast cancer, overall and stratified by the age at first breast cancer.

Table 4: Hazard Ratio estimates for breast and ovarian cancer associated with family history of breast or ovarian cancer in first- and second-degree relatives or with mutation location and corresponding cumulative risk estimates.

eTable 1: Number of samples from each study.

eTable 2: Completeness of follow-up and sources of information for censoring endpoints, for the samples included in the breast cancer analysis

eTable 3: Breast cancer incidence rates per 1000 person-years, Kaplan-Meier estimates of the cumulative risks and Standardised Incidence Rates when censoring for risk-reducing salpingo-oophorectomy, by 10-year age groups

eTable 4: Breast cancer incidence rates per 1000 person-years and Kaplan-Meier estimates of the cumulative risks, considering only invasive breast cancer.

eTable 5: Breast cancer incidence rates per 1000 person-years and Kaplan-Meier estimates of the cumulative risks, by 10-year age groups, by study groupings.
eTable 6: Breast cancer incidence rates per 1000 person-years and Kaplan-Meier estimates of the cumulative risks, by 10-year age groups, by study ascertainment type: family clinic vs population-based studies.

eTable 7: Contralateral breast cancer incidence rates per 1000 person-years and Kaplan-Meier estimates of the cumulative risks, by 10-year age groups, overall and stratified by age at unilateral breast cancer (UBC).

eTable 8: Contralateral breast cancer incidence rates per 1000 person-years and Kaplan-Meier estimates of the cumulative risks when censoring for risk-reducing Salpingo-oophorectomy, by 10-year age groups and time since first breast cancer diagnosis.

eTable 9: Hazard Ratio estimates for breast and ovarian cancer associated with family history of breast or ovarian cancer in first degree relatives.

eTable 10: Hazard Ratio estimates for breast cancer associated with family history of breast cancer in first and second degree relatives, stratified by presence of ovarian cancer family history.

eTable 11: Hazard Ratio estimates for ovarian cancer associated with family history of ovarian cancer in first and second degree relatives, stratified by presence of breast cancer family history.

eTable 12: Hazard Ratio estimates for breast cancer associated with family history of ovarian cancer in first and second degree relatives, stratified by presence of breast cancer family history.

eTable 13: Hazard Ratio estimates for ovarian cancer associated with family history of breast cancer in first and second degree relatives, stratified by presence of ovarian cancer family history.
eTable 14: Sensitivity analyses: hazard ratio estimates for breast cancer associated with mutation location, adjusted for family history of breast cancer in first and second-degree relatives or by excluding the Ashkenazi mutations (BRCA1: c.68_69delAG and c.5266dupC; BRCA2: c.5946delT)