Second primary cancer risks following breast cancer in *BRCA1* and *BRCA2* pathogenic variant carriers

Running head - Cancer risks in *BRCA1* and *BRCA2* carriers post-breast cancer

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Manuscript data

Declarations of interests

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Originality statement:

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Author contributions

IA drafted the manuscript and performed the analyses. IA, LL, HH, and MT selected the censoring surgeries. TR, AB, CK, and SJ collected and verified the data. FM, JP, FS, SA and LL readied the genetic dataset following laboratory submissions. SA and AG developed the pipeline to infer pathogenic classes of genetic variants. HH developed the multiple imputation approach. ACA, PP, MT and CT

conceived of the study and raised funding. MT, PP and ACA supervised the project and reviewed and edited the manuscript drafts. All authors provided feedback to inform the research and analysis.

Data sharing statement

This work uses data provided by patients and collected by the National Health Service as part of their care and support. The data are collated, maintained and quality assured by the National Disease Registration Service, which is part of the National Health Service England. Data in this manuscript may be accessed through application to the National Health Service England.

Context summary

Key objective

Second primary cancer (SPC) risks following breast cancer (BC) in *BRCA1/BRCA2* pathogenic variant (PV) carriers are unclear. This study investigates associations between *BRCA1/BRCA2* PVs and SPCs in a novel, population-scale linkage of electronic health records from the National Health Service England and genetic testing data from clinical laboratories across England.

Knowledge generated

Elevated risks were found for SPCs at the contralateral breast/ovary in female *BRCA1/BRCA2* PV carriers, colorectum in female *BRCA1* PV carriers, pancreas in female *BRCA2* PV carriers, and contralateral breast/prostate in male *BRCA2* PV carriers. Risks were particularly elevated in females younger at first BC diagnosis.

Abstract

Purpose

Second primary cancer (SPC) risks following breast cancer (BC) in *BRCA1/BRCA2* pathogenic variant (PV) carriers are uncertain. We estimated relative and absolute risks using a novel linkage of genetic testing data to population-scale National Disease Registration Service and Hospital Episode Statistics electronic health records.

Methods

We followed 25,811 females and 480 males diagnosed with BC and tested for germline *BRCA1/BRCA2* PVs in NHS Clinical Genetics centres in England between 1995-2019 until SPC diagnosis, death, migration, contralateral breast/ovarian surgery plus one year, or the 31st of December 2020. We estimated Standardized Incidence Ratios (SIRs) using English population incidences, Hazard Ratios (HRs) comparing carriers to non-carriers using Cox regression, and Kaplan-Meier 10-year cumulative risks.

Results

There were 1840 *BRCA1* and 1750 *BRCA2* female PV carriers. Compared to population incidences, *BRCA1* carriers had elevated contralateral breast cancer (CBC) (SIR:15.6, 95%CI:11.8-20.2), ovarian (SIR:44.0, 95%CI:31.4-59.9), combined non-breast/ovarian (SIR:2.18, 95%CI:1.59-2.92), colorectal (SIR:4.80, 95%CI:2.62-8.05), and endometrial (SIR:2.92, 95%CI:1.07-6.35) SPC risks. *BRCA2* carriers had elevated CBC (SIR:7.70, 95%CI:5.45-10.6), ovarian (SIR:16.8, 95%CI:10.3-26.0), pancreatic (SIR:5.42, 95%CI:2.09-12.5), and combined non-breast/ovarian (SIR:1.68, 95%CI:1.24-2.23) SPC risks. Compared to females without *BRCA1/BRCA2* PVs on testing, *BRCA1* carriers had elevated CBC (HR:3.60, 95%CI:2.65-4.90), ovarian (HR:33.0, 95%CI:19.1-57.1), combined non-breast/ovarian (HR:1.45, 95%CI:1.05-2.01), and colorectal (HR:2.93, 95%CI:1.53-5.62) SPC risks. *BRCA2* carriers had elevated CBC (HR:2.40, 95%CI:1.70-3.40), ovarian (HR:12.0, 95%CI:6.70-21.5), and pancreatic (HR:3.56, 95%CI:1.34-9.48) SPC risks. 10-year cumulative CBC, ovarian, and combined non-

breast/ovarian cancer risks were 16%/6.3%/7.8% (*BRCA1* carriers), 12%/3.0%/6.2% (*BRCA2* carriers), and 3.6%/0.4%/4.9% (non-carriers). Male *BRCA2* carriers had higher CBC (HR:13.1, 95%CI:1.19-146) and prostate (HR:5.61, 95%CI:1.96-16.0) SPC risks than non-carriers.

Conclusion

BC survivors carrying BRCA1 and BRCA2 PVs are at high SPC risk. They may benefit from enhanced surveillance and risk-reduction measures.

Background

BRCA1 (BReast Cancer gene 1) and *BRCA2* (BReast Cancer gene 2) pathogenic variant (PV) prevalences in females diagnosed with BC have been estimated as 1.1% and 1.5% respectively (1). BC survivors found to carry *BRCA1* and *BRCA2* PVs are likely to increase in number due to the increasing frequency of genetic testing in oncology (2) and good survival outcomes, with 15-year BC-specific survival rates estimated as around 81% in *BRCA1* and 75% in *BRCA2* PV carriers (3). Second primary cancer (SPC) risks for *BRCA1* and *BRCA2* PV carriers remain uncertain. Studies reporting non-breast (4–6) or contralateral breast cancer (CBC) risks (3,6–8) are limited in number and size. Precise estimates could inform cancer surveillance and risk reduction options for BC survivors carrying *BRCA1/BRCA2* PVs. Although male BC is rare (9), *BRCA2* PV prevalence among male BC patients is high (8.1%) (10). To our knowledge, no study has estimated SPC risks following BC in male PV carriers.

We performed a novel linkage of the National Cancer Registration dataset (NCRD) (11), Hospital Episode Statistics Admitted Patient Care (HES APC) (12) and outpatients (HES OP) (13) datasets, and individual-level germline testing information from regional molecular genetics laboratories across England (14) (henceforth 'germline testing dataset'). We describe these datasets in the Data Supplement. We established a cohort of individuals diagnosed with BC and tested for *BRCA1* or *BRCA2* PVs through NHS Clinical Genetics centres in England. We estimated relative and absolute SPC risks at combined and specific sites for *BRCA1/BRCA2* PV carriers following a BC diagnosis. We investigated how these risks varied by age at diagnosis, and oestrogen receptor (ER) status, of the first BC.

Methods

Study population

We constructed the retrospective cohort using data on all individuals diagnosed with invasive, non-metastatic BC between 1st January 1995 and 31st December 2019 in England, linked to *BRCA1/BRCA2* PV germline testing data submitted by 16 National Health Service (NHS) molecular genetic laboratories in England. Testing eligibility was based on established guidelines for the same period

(15). Cohort eligibility was restricted to those with genetic testing information. Surgery data were extracted from the HES APC/OP datasets. Data on death, cancer diagnoses, gender, sociodemographic factors, treatments, and embarkation were drawn from the NCRD. Data on genes tested, pathogenic classes, test dates, coding DNA sequence changes and protein impact of variants, and genetic test free text records were drawn from the germline testing dataset. Pseudonymized patient data were linked using unique tumour and patient identifiers. Consent from subjects was not required as these data are collected by NHS England (NHSE) under Section 254 of the Health and Social Care Act 2012. Ethical approval for the data analyses was granted to the CanGene-CanVar research programme (REC:18/WS/0192).

Defining *BRCA1* and *BRCA2* pathogenic variant carrier status

We divided the cohort into *BRCA1* PV carriers, *BRCA2* PV carriers, *BRCA1/BRCA2* PV non-carriers, and those of other *BRCA1/BRCA2* PV status (Data Supplement, Table S1). BC survivors were predominantly assigned other carrier status due to being untested for PVs in one of the genes or missing test results (Data Supplement). We do not present analyses for this group unless stated otherwise.

Statistical analyses

Follow-up began at the latest of the *BRCA1* PV test date, *BRCA2* PV test date, and 365 days following the BC diagnosis, and continued until the next cancer diagnosis, death, migration, contralateral breast/ovarian surgery plus one year (Data Supplement, Table S2), or the 31st of December 2020. We did not consider cancers diagnosed from death certificates, ipsilateral BCs, CBCs diagnosed less than 93 days following the first BC, and non-melanoma skin cancers as SPCs, so follow-up continued following these diagnoses when applicable. We defined cancer sites using the ICD-10 code groups employed by Cancer Research UK (16) (Data Supplement, Table S3).

Comparison of SPC risks for PV carriers relative to population risks

To compare cancer incidences in *BRCA1/BRCA2* PV carriers following BC to population incidences, we estimated ratios of observed to expected SPCs (standardized incidence ratios (SIRs)) separately by *BRCA1/BRCA2* PV carrier status for SPCs at the contralateral breast, ovary, all non-breast/ovarian sites combined, and any other site where at least 3 cancers were observed in *BRCA1* or *BRCA2* PV carriers. The expected counts were calculated using age-, calendar year-, gender-, and site-specific incidence rates for the English population (17), whom predominantly had no cancer history. We filtered cancers diagnosed from death certificates and non-melanoma skin cancers from the expected counts. In females, we stratified SIRs by age at BC diagnosis (Under 45 years/45 years or over) and first BC ER status (positive/negative), as both are associated with *BRCA1/BRCA2* PV carrier status (8,18) and SPC risks (19).

Comparison of SPC risks for *BRCA1* and *BRCA2* PV carriers relative to non-carriers

SIRs estimate SPC risks in BC survivors carrying *BRCA1/BRCA2* PVs relative to the general population. Therefore, they reflect risk alterations conferred by the first BC, *BRCA1/BRCA2* PVs, and genetic testing selection criteria such as cancer family history (FH) (20). To compare SPC risks in BC survivors carrying PVs to BC survivors tested negative for PVs in both genes, we estimated Hazard Ratios (HR)s for SPCs at all sites with significantly elevated SIR estimates for *BRCA1* or *BRCA2* carriers, using Cox proportional hazards models. For females, we adjusted these models for age and calendar year at BC diagnosis and ER status of the first BC, where missing ER status data were imputed using multiple imputation by chained equations (21) (Data Supplement). As a sensitivity analysis, we further adjusted these models for receipt of chemotherapy, radiotherapy, and hormonal therapy. As a separate sensitivity analysis, we included females untested for a PV in one gene and confirmed not to carry a PV in the other gene following predictive testing in the non-carrier group rather than the 'Other' carrier group. We performed these sensitivity analyses when estimating HRs for CBC, OC, and non-breast/ovarian cancer, but not for other SPCs due to low event counts. For males, we included only PV carrier status (*BRCA2* PV carrier or *BRCA1* and *BRCA2* PV non-carrier) in the models due to low sample sizes. To assess whether the effect of a *BRCA1* PV on CBC risk was modified by age at first BC diagnosis in females, we fit a Cox model including an interaction term between continuous age at first BC diagnosis and PV carrier status (separately for *BRCA1* and *BRCA2*) and compared this to the corresponding original model by performing likelihood ratio tests in each imputed dataset and comparing the pooled test statistic to an F-distribution (21). We tested whether the effect of *BRCA1*

or *BRCA2* PVs on CBC, ovarian cancer (OC) and combined non-breast/ovarian cancer risks were modified by age at first BC diagnosis, year at first BC diagnosis, and first BC ER status in females analogously. We assessed the proportional hazards assumption by inspecting transformed survival functions (Data Supplement, Figure S9-S11).

Incidence rates and cumulative risks

In females, we estimated 10-year cumulative CBC, OC, and combined non-breast/ovarian SPC risks using Kaplan-Meier techniques. We estimated incidences per 10,000 person-years (py) for these cancers between 0-5 years and 5-10 years of follow-up. We also estimated the corresponding incidences during a 5-year follow-up period, stratified by year at first BC diagnosis (before 2013/2013 or after). All analyses were stratified by carrier status.

We conducted all analyses in R version 4.3.1 (22) (packages in Data Supplement).

Results

Unless stated otherwise, results refer to females.

Cohort description

The cohort included 1840 *BRCA1* PV carriers, 1750 *BRCA2* PV carriers, and 21,543 non-carriers (Figure 1). Median age at first BC diagnosis was 39 (interquartile range (IQR):14 years) in *BRCA1* carriers, 45 (IQR:14 years) in *BRCA2* PV carriers, and 46 (IQR:15 years) in non-carriers. Corresponding median follow-up lengths were 3.5 years (IQR:4.4 years), 3.8 years (IQR:4.3 years), and 3.5 years (IQR:3.8 years). CBC was the commonest cancer in all groups (*BRCA1* PV carriers:66 events, *BRCA2* PV carriers:43 events, non-carriers:237 events). The cohort was primarily of White ethnicity (*BRCA1* PV carriers:82%, *BRCA2* PV carriers:90%, non-carriers:87%). Among those with available ER status data, 71% of *BRCA1* PV carriers, 26% of *BRCA2* PV carriers, and 38% of non-carriers had ER-negative first BC. The majority of the cohort received chemotherapy (*BRCA1* PV carriers:81%, *BRCA2* PV carriers:68%, non-carriers:64%) and radiotherapy (*BRCA1* PV carriers:52%, *BRCA2* PV carriers:55%,

non-carriers:66%) and did not receive hormonal therapy (*BRCA1* PV carriers:86%, *BRCA2* PV carriers:70%, non-carriers:74%) by one-year post-BC diagnosis. By the end of follow-up, most *BRCA1/BRCA2* PV carriers had received contralateral breast surgery (*BRCA1* PV carriers:64%, *BRCA2* PV carriers:61%, non-carriers:22%) and bilateral ovarian surgery (*BRCA1* PV carriers:55%, *BRCA2* PV carriers:62%, non-carriers:10%). Further descriptives are in Table 1 and the Data Supplement (Table S4, Table S12, Figure S1-S4).

Among males, there were 7 *BRCA1* PV carriers, 74 *BRCA2* PV carriers, and 394 non-carriers. They had 0, 15, and 23 SPCs, respectively. Further descriptives are in the Data Supplement (Table S5-S6, Table S13, Figure S5-S8).

Comparison of SPC risks for PV carriers relative to population risks

Compared to population-level incidences, PV carriers were at elevated CBC (*BRCA1*: SIR:15.6, 95%CI:11.8-20.2. *BRCA2*: SIR:7.70, 95%CI:5.45-10.6) and OC (*BRCA1*: SIR:44.0, 95%CI:31.4-59.9. *BRCA2*: SIR:16.8, 95%CI:10.3-26.0) risks. The magnitudes of both increases were higher in *BRCA1* than *BRCA2* PV carriers (Table 2). *BRCA1/BRCA2* PV carriers had elevated combined non-breast/ovarian cancer SIRs (*BRCA1*: SIR:2.18, 95%CI:1.59-2.92. *BRCA2*: SIR:1.68, 95%CI:1.24-2.23). Colorectal (SIR:4.80, 95%CI:2.62-8.05) and endometrial (SIR:2.92, 95%CI:1.07-6.35) cancer SIRs were increased in *BRCA1* PV carriers. The pancreatic cancer SIR was elevated in *BRCA2* PV carriers (SIR:5.72, 95%CI:2.09-12.5).

The CBC SIR was higher in *BRCA1* PV carriers first diagnosed with BC at under age 45 than at 45 or over (Under 45: SIR:23.5, 95%CI:16.6-32.3. 45 or over: SIR:9.31, 95%CI:5.60-14.5). There was no clear difference in CBC SIRs by age at first BC diagnosis in *BRCA2* PV carriers, although SIRs were elevated in both groups (Under 45: SIR:9.58, 95%CI:5.10-16.4. 45 or over: SIR:6.99, 95%CI:4.52-10.3). There were no clear differences by age at first BC diagnosis in SPC SIRs at other sites in *BRCA1/BRCA2* PV carriers.

Non-carriers had elevated CBC and non-breast/ovarian cancer SIRs, which were lower than the corresponding *BRCA1*- or *BRCA2*-specific SIRs (CBC: SIR:3.03, 95%CI:2.67-3.43, Non-breast/ovarian:

SIR:1.26, 95%CI:1.14-1.38). The CBC SIR was more elevated in those diagnosed with BC at under age 45 (Under 45: SIR:4.50, 95%CI:3.70-5.41. 45 or over: SIR:2.43, 95%CI:2.05-2.86). There was a modest increased endometrial cancer SIR in non-carriers (SIR:1.43, 95%CI:1.06-1.89), and no significant evidence for increased ovarian, colorectal, or pancreatic cancer SIRs. There was some evidence for a non-breast/ovarian cancer risk difference by age at first BC diagnosis in non-carriers (Under 45: SIR:1.68, 95%CI:1.39-2.01. 45 or over: SIR:1.15, 95%CI:1.02-1.28), which we did not observe for *BRCA1/BRCA2* PV carriers.

We observed no clear SPC SIR differences by first BC ER status at any site, in any carrier group.

Male *BRCA2* PV carriers had elevated CBC (SIR:431, 95%CI:48.5-1559), pancreatic (SIR:20.2, 95%CI:4.07-59.1), and prostate (SIR:4.46, 95%CI:1.79-9.19) cancer SIRs. No SIRs were significantly elevated in non-carriers (Data Supplement, Table S7).

Comparison of SPC risks between PV carriers and non-carriers

BRCA1 PV carriers were at increased CBC (HR:3.60, 95%CI:2.65-4.90), OC (HR:33.0, 95%CI:19.1-57.1), colorectal (HR:2.93, 95%CI:1.53-5.62), and non-breast/ovarian (HR:1.45, 95%CI:1.05-2.01) cancer risks compared to non-carriers (Table 3). *BRCA2* PV carriers were at increased CBC (HR:2.40, 95%CI:1.70-3.40), ovarian (HR:12.0, 95%CI:6.70-21.5), and pancreatic (HR:3.56, 95%CI:1.34-9.48) cancer risks. There was no significant evidence for interactions between age at diagnosis, year at diagnosis, or ER status of the first BC with *BRCA1* or *BRCA2* PV carrier status when evaluating associations with CBC, OC, or non-breast/ovarian cancer risks. CBC, OC, and non-breast/ovarian cancer HRs remained similar after adjusting for chemotherapy, radiotherapy, and hormonal therapy (Data Supplement, Table S9), and after including females that tested negative for a PV in one gene following predictive testing, and were untested for PVs in the other gene, in the *BRCA1/BRCA2* PV non-carrier group (Data Supplement, Table S10).

Male *BRCA2* PV carriers had higher CBC and prostate SPC risks than *BRCA1/BRCA2* PV non-carriers (CBC: HR:13.1, 95%CI:1.19-146. Prostate: HR:5.61, 95%CI:1.96-16.0) (Data Supplement, Table S8).

Incidence rates and cumulative risks

The ten-year cumulative CBC risks were 16% (95%CI:8.7%-22%) in *BRCA1* PV carriers, 12% (95%CI:6.5%-18%) in *BRCA2* PV carriers, and 3.6% (95%CI:2.9%-4.2%) in non-carriers. The corresponding OC and combined non-breast/ovarian SPC risks were 6.3% (95%CI:2.8%-9.7%), 3.0% (95%CI:1.3%-4.6%), and 0.4% (95%CI:0.1%-0.6%) and 7.8% (95%CI:4.6%-11%), 6.2% (95%CI:3.6%-8.7%), and 4.9% (95%CI:4.2%-5.6%). Ten-year cumulative risk and incidence estimates can be seen in Table 4, with 10-year Kaplan-Meier curves visible in Figure 2.

Within each carrier group, the incidence estimates during a 5-year period for CBC, OC, and non-breast/ovarian cancer were somewhat higher for those diagnosed with their first BC before 2013 than those diagnosed in 2013 or later (Table S11).

Discussion

This study is one of the first to examine non-breast cancer risks (4–6) and one of the largest to examine CBC risks (3,7,8) following BC in female *BRCA1/BRCA2* PV carriers. It is the first to investigate associations between germline pathogenic variation and SPC risks following male BC. It is the first study based on a linkage of germline testing laboratory data to population-scale electronic health records (EHRs), minimising selection biases common in recruitment-based PV carrier cohort studies (23). It is based on very high-quality registry data (11–14). This work offers proof of principle that linkages of genetic testing laboratory data to population-scale EHRs allow estimation of understudied cancer risks in novel cohorts.

In females, we found elevated CBC, ovarian, and non-breast/ovarian SPC risks in *BRCA1/BRCA2* PV carriers, colorectal and endometrial SPC risks in *BRCA1* PV carriers, and pancreatic SPC risks in *BRCA2* PV carriers, relative to the general English population, as measured by the SIRs. These increased SIRs cannot be fully attributed to *BRCA1/BRCA2* PVs as some of the increase will reflect the effect of cancer risk factors associated with having survived a first BC, such as common genetic variation (24,25) and non-genetic factors such as treatment effects (19,26). The ascertainment process will also partly explain the elevated SIRs, as those tested for *BRCA1/BRCA2* PVs are typically highly

selected based on criteria such as cancer FH (20). Nevertheless, the *BRCA1/BRCA2* SIR estimates were much higher than the corresponding SIRs for non-carriers, and the HR estimates comparing carriers and non-carriers were elevated at most sites with increased SIR estimates. Since the carrier and non-carrier groups in the HR estimations were ascertained in similar fashions and composed of BC survivors, the effects of the ascertainment process and BC-associated SPC risk factors will likely be attenuated when comparing carriers to non-carriers. This suggests that much of the excess SPC risks are attributable to *BRCA1/BRCA2* PVs. However, the HR estimates may be biased if cancer FH differs between carriers and non-carriers in this cohort. Unfortunately, cancer FH data were unavailable. Notably, the female CBC HR estimates for both *BRCA1* and *BRCA2* PV carriers were consistent with two recent cohort studies (3,7).

We found higher CBC SIRs for female *BRCA1* PV carriers aged under 45 at first BC diagnosis compared to those diagnosed when older. This is consistent with population-level observations (19) and could be explained by the higher proportion of ER-negative breast cancer (18,19) or more extensive BC FH (26,27) in *BRCA1* PV carriers younger at BC diagnosis. We found no other notable SIR differences by age at first BC diagnosis in *BRCA1/BRCA2* PV carriers.

The 10-year cumulative CBC, OC, and non-breast/ovarian cancer risk estimates are applicable to carriers and tested non-carriers ascertained through clinical genetics centres, and the CBC risk estimates for *BRCA1/BRCA2* PV carriers were broadly consistent with a large previous study with similar ascertainment criteria (8). However, they would overestimate the risks in *BRCA1/BRCA2* PV carriers unselected for cancer FH, emphasising the importance of integrating FH in the counselling and risk estimation process (20).

The male *BRCA2* PV carrier CBC SIR was greater than the corresponding HR, indicating that FH may partly account for the elevated risk, as consistent with previous research (28). The prostate cancer SIR was consistent with prior research (29), and similar to the corresponding HR.

The SIR, HR, and cumulative risk estimates in *BRCA1/BRCA2* PV carriers may be inflated by surveillance bias, as cancer surveillance may be heightened following a positive *BRCA1/BRCA2* PV test (20). The SIR estimates may be additionally prone to such bias owing to heightened surveillance

in BC survivors relative to the general population (20). In addition, the low non-breast/ovarian/prostate SPC counts may mean some analyses were underpowered, particularly in males. Furthermore, the median follow-up of under 4 years and median age of 46 at first BC diagnosis may have precluded the identification of associations with later- or older-onset cancers. Finally, since the criteria for a genetic testing referral changed in 2013 (30), the influence of FH on the estimates may differ between those tested for before 2013 and in 2013 or later. Analyses were adjusted for first BC diagnosis year when estimating HRs and SIRs. However, the absolute incidence estimates were somewhat higher for those diagnosed before 2013 than those diagnosed in 2013 or later. This may also reflect improvements in clinical management over time (Data Supplement, Table S11).

The elevated CBC/OC cancer risks, together with previous results (3,5,7,8), suggest that females found to carry *BRCA1/BRCA2* PVs may wish to consider risk-reducing options such as contralateral mastectomy and risk-reducing bilateral salpingo-oophorectomy following BC. These recommendations are consistent with results from previous studies (31,32).

We also found increased CBC and prostate cancer risks in male *BRCA2* PV carriers and elevated colorectal and pancreatic cancer risks in female *BRCA1* and *BRCA2* PV carriers. Although these results were based on low SPC counts, previous findings of elevated first primary risks at the breast and prostate in male *BRCA2* PV carriers, colorectal cancer in female *BRCA1* PV carriers, and pancreatic cancer in female *BRCA2* PV carriers (33) suggest these associations may be true.

In conclusion, we estimated combined and site-specific relative and absolute SPC risks in *BRCA1/2* PV carriers following BC. We investigated risk variability by age at diagnosis and ER status of the first BC in females. This study demonstrates the value of population-scale EHR linkages, and that BC survivors carrying *BRCA1/BRCA2* PVs are at elevated cancer risks.

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