The impact of coding germline variants on contralateral breast cancer risk and survival

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Protein-truncating and/or (likely) pathogenic missense variants in *BRCA1*, *BRCA2*, *CHEK2*, *PALB2*, and *TP53* were associated with 2- to 8-fold higher risk of contralateral breast cancer. Associations with breast cancer-specific survival were generally weaker. These findings are relevant to treatment decisions, follow-up, and screening after breast cancer diagnosis.

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The impact of coding germline variants on contralateral breast cancer risk and survival

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Summary

Evidence linking coding germline variants in breast cancer (BC)-susceptibility genes other than *BRCA1*, *BRCA2*, and *CHEK2* with contralateral breast cancer (CBC) risk and breast cancer-specific survival (BCSS) is scarce. The aim of this study was to assess the association of protein-truncating variants (PTVs) and rare missense variants (MSVs) in nine known (*ATM*, *BARD1*, *BRCA1*, *BRCA2*, *CHEK2*, *PALB2*, *RAD51C*, *RAD51D*, and *TP53*) and 25 suspected BC-susceptibility genes with CBC risk and BCSS. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated with Cox regression models. Analyses included 34,401 women of European ancestry diagnosed with BC, including 676 CBCs and 3,449 BC deaths; the median follow-up was 10.9 years. Subtype analyses were based on estrogen receptor (ER) status of the first BC. Combined PTVs and pathogenic/likely pathogenic MSVs in *BRCA1*, *BRCA2*, and *TP53* and PTVs in *CHEK2* and *PALB2* were associated with increased CBC risk [HRs (95% CIs): 2.88 (1.70–4.87), 2.31 (1.39–3.85), 8.29 (2.53–27.21), 2.25 (1.55–3.27), and 2.67 (1.33–5.35), respectively]. The strongest evidence of association with BCSS was for PTVs and pathogenic/likely pathogenic MSVs in *BRCA2* (ER-positive BC) and *TP53* and PTVs in *CHEK2* [HRs (95% CIs): 1.53 (1.13–2.07), 2.08 (0.95–4.57), and 1.39 (1.13–1.72), respectively, after adjusting for tumor characteristics and treatment]. HRs were essentially unchanged when censoring for CBC, suggesting that these associations are not completely explained by increased CBC risk, tumor characteristics, or treatment. There was limited evidence of associations of PTVs and/or rare MSVs with CBC risk or BCSS for the 25 suspected BC genes. The CBC findings are relevant to treatment decisions, follow-up, and screening after BC diagnosis.

Introduction

Breast cancer (BC [MIM: 114480])-susceptibility genes may modulate BC prognosis. Studies of unselected young women diagnosed with invasive breast tumors showed worse survival for *BRCA1/2* (*BRCA1* [MIM: 113705]; *BRCA2* [MIM: 600185]) mutation carriers compared with non-carriers.[1,2] On the other hand, a large meta-analysis

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concluded that differences in breast cancer-specific survival (BCSS) by carrier status in the adjuvant setting are likely to be small.[3] Poorer prognosis has also been reported in carriers of the *CHEK2* (MIM: 604373) c.1100delC variant[4–6] (GenBank: NM_007194.4) (p.Thr367fs*15) and of some pathogenic *PALB2*[7,8] (MIM: 610355) variants. Evidence linking other putative BC-risk genes with prognosis is scarce.

Germline genetic variants could affect prognosis by predisposing to an aggressive BC subtype, by impairing BC treatment response, or by increasing the risk of a second primary BC.[1,9–13] These variants could also influence immune responses to the tumor.[14–17] Recently, a large study,[18] BRIDGES, investigated coding germline genetic variants in a panel of 34 genes, providing strong evidence for association with nine of these genes with risk of developing a first primary BC. Using the BRIDGES data, we mainly aimed to investigate the association of protein-truncating variants (PTVs) and rare missense variants (MSVs) in the nine known BC-susceptibility genes (*ATM* [MIM: 607585], *BARD1* [MIM: 601593], *BRCA1*, *BRCA2*, *CHEK2*, *PALB2*, *RAD51C* [MIM: 602774], *RAD51D* [MIM: 602954], and *TP53* [MIM: 191170]) with BCSS and with risk of developing a contralateral breast cancer (CBC). Our secondary goal was to evaluate the evidence of associations of PTVs and rare

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MSVs with CBC risk and BCSS in the remaining 25 suspected BC-risk genes on the BRIDGES panel.

Material and methods

Study sample

We selected women of European ancestry from studies participating in the Breast Cancer Association Consortium (BCAC). In particular, ancestry was defined on the basis of array genotype data if available,[19] or self-reported. Women were included if diagnosed with a primary invasive BC without known distant metastases, were between 18 and 79 years of age (median: 56; interquartile range [IQR]: 48–64) in the period 1942–2018 (median: 2003; IQR: 1999–2006), and had available information on vital status and number of years from diagnosis to last follow-up. Our final study sample consisted of 34,401 women from 34 BCAC studies (Tables S1, S2, and S3): 28 population or hospital-based and six family or clinical genetic center based.

Information on tumor characteristics, pathology, CBC, survival, and treatment was collected by individual studies, pooled, and harmonized (BCAC database: version 13, November 2020). The BCAC database did not include information about preventive contralateral mastectomy and oophorectomy.

All studies were approved by the pertinent ethics committees and informed consent was obtained from all study participants.

Sequencing and variant classification

DNA of participants was collected through the individual studies and collated for panel sequencing. Laboratory methods, including calling and classification of PTVs and MSVs, have been described elsewhere.[18]

Statistical analyses

Statistical analyses were performed by gene, for PTVs in aggregate and rare MSVs (allele frequency < 0.001)[18] in aggregate. More specifically, individual study subjects were considered as carriers of PTVs in a given gene if they carried at least one PTV in that given gene. The same was done for rare MSVs. Carriers of PTVs in a given gene were excluded from the analyses of rare MSVs of that specific gene. In addition, MSVs in aggregate in *BRCA1*, *BRCA2*, and *TP53* determined to be likely pathogenic, as previously described,[18] were also analyzed (supplemental methods). For *BRCA1*, *BRCA2*, and *TP53* pathogenic/likely pathogenic MSVs were combined with PTVs in the analyses. This was done in consideration of the previous evidence that pathogenic/likely pathogenic MSVs in *BRCA1* and *BRCA2* have similar BC risk as PTVs,[18] while MSVs in *TP53* are well established to contribute to risk.[20]

Missing values in clinical and pathological variables related to the first BC (Table S4) were imputed with the MICE R package (v.3.13.0). Details are provided in the supplemental methods and Table S5.

The primary outcomes were time to development of a CBC and BCSS (time to death due to BC). Overall survival (time to death due to any cause) analyses were performed as sensitivity analyses because several genes on the BRIDGES panel are associated with different cancers or other diseases.[18]

We used delayed-entry Cox regression models stratified by country to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) and we performed them by using the R package "survival."[21,22] Standard errors of the HR estimates were re-computed on the basis of the likelihood ratio test statistic.[23]

CBC risk analyses were based on women with known CBC status and, for women who developed a CBC, time from diagnosis of the first BC to CBC. In particular, women with missing time from first BC to CBC diagnosis (43 out of the 1,523 CBCs reported in Table S4), women diagnosed with a CBC within 3 months after diagnosis of the first BC (492 out of 1,523), and women who developed a CBC before study entry (312 out of 1,523) were excluded from the CBC risk analyses. All CBCs were considered, including invasive (70.7%), *in situ* (10.9%), and those with unknown invasive versus *in situ* status (18.3%). For these analyses, time at risk started either at 3 months after the diagnosis of the first BC or at study entry if study entry was more than 3 months after the diagnosis of the first BC and ended at time of CBC, death, or last follow-up, whichever came first.

For BCSS and overall survival analyses, time-to-event started at diagnosis of the first BC and ended at time of death or last follow-up; time at risk started at study entry if this was after diagnosis of a first BC. For BCSS analyses, women who died from unknown cause or cause other than BC were censored at time of death or otherwise at last follow-up. Additional BCSS analyses were performed where women diagnosed with a CBC were censored at time of CBC diagnosis. Women known to have developed a CBC before study entry were excluded from the main survival analyses.

Main CBC risk and BCSS analyses were also performed by estrogen receptor (ER) status of the first BC. Subtype analyses included only women with non-missing ER status. Heterogeneity of HR estimates by ER status was tested, as explained in the supplemental methods.

In addition to the unadjusted analyses, comparing carriers to non-carriers of PTVS or rare MSVs in a given gene, adjusted analyses were performed including age at diagnosis and characteristics of the first BC and systemic treatment as covariates. In particular, systemic treatment was defined as having received endocrine therapy, any kind, (yes versus no), trastuzumab (yes versus no), and neo-adjuvant and/or adjuvant chemotherapy (yes versus no). The aim of the adjusted analyses was to assess to what extent the impact of PTVs or rare MSVs in a given gene on CBC risk and survival could be explained through other established prognostic factors. We performed these analyses on imputed covariates to keep the same sample size.

For each gene, the set of non-carriers included women who did not carry any of the identified PTVs or rare MSVs for that specific gene, irrespective of whether they were carriers of a PTV or rare MSV in any other gene. For CBC risk, sensitivity analyses were performed restricting the set of non-carriers to those women who did not carry PTVs in any of the nine main BC-susceptibility genes or pathogenic/likely pathogenic MSVs for *BRCA1*, *BRCA2*, and *TP53*. Since early age at onset has been shown to influence CBC risk in *BRCA1/2* and *TP53* carriers,[24–26] unadjusted CBC risk analyses were performed separately for combined PTVs and pathogenic/likely pathogenic MSVs in *BRCA1*, *BRCA2*, and *TP53* within subgroups of women diagnosed with first BC at age younger than 40 years and at age equal to or older than 40 years. Heterogeneity of HR estimates by age at onset of first BC was tested as explained in the supplemental methods.

Additional sensitivity analyses were performed with data from cohort, population-based, and hospital-based studies, excluding studies that selected women with family history of BC or women from studies that partially selected individuals with family history of BC (Table S1).

CBC cumulative incidence estimates for the nine known BC-susceptibility genes, allowing for competing risk of death (Figures 2 and S1), were computed as specified in the supplemental methods. Kaplan-Meier curves for BCSS are shown in Figure S2.

Table 1. Association of protein-truncating variants in nine breast cancer genes and of pathogenic/likely pathogenic rare missense variants in *BRCA1*, *BRCA2*, and *TP53* with risk of contralateral breast cancer

Gene	Unadjusted analyses		Adjusted analyses[a]		No. of women		No. of CBC	
PTVs (unless indicated otherwise)	HR (95% CI)	p	HR (95% CI)	p	Non-carriers	Carriers	Non-carriers	Carriers
ATM	1.13 (0.50–2.58)	7.7E−01	1.17 (0.51–2.70)	7.1E−01	30,399	229	670	6
BARD1	1.97 (0.42–9.27)	3.9E−01	1.89 (0.40–8.85)	4.2E−01	30,577	51	674	2
BRCA1[b]	2.84 (1.71–4.72)*	5.7E−05*	2.88 (1.70–4.87)*	8.8E−05*	30,298	330	655	21
BRCA2[b]	2.31 (1.39–3.82)*	1.2E−03*	2.31 (1.39–3.85)*	1.3E−03*	30,208	420	656	20
CHEK2	2.24 (1.55–3.25)*	1.8E−05*	2.25 (1.55–3.27)*	2.2E−05*	29,972	656	638	38
c.1100delC	2.42 (1.63–3.59)*	1.2E−05*	2.43 (1.63–3.62)*	1.5E−05*	29,972	530	638	34
Other	1.40 (0.49–3.94)	5.3E−01	1.40 (0.49–3.96)	5.3E−01	29,972	126	638	4
PALB2	2.63 (1.32–5.24)*	6.0E−03*	2.67 (1.33–5.35)*	5.6E−03*	30,428	200	665	11
RAD51C	2.20 (0.46–10.58)	3.3E−01	2.21 (0.46–10.72)	3.2E−01	30,591	37	674	2
RAD51D	1.68 (0.20–14.12)	6.4E−01	1.47 (0.18–11.93)	7.2E−01	30,599	29	675	1
TP53[b]	7.98 (2.46–25.89)*	5.4E−04*	8.29 (2.53–27.21)*	5.1E−04*	30,587	41	671	5

Abbreviations: No., number; CBC, contralateral breast cancer; PTVs, protein-truncating variants; HR, hazard ratio; CI, confidence interval; p, p value. Analyses included women from 32 studies with information about contralateral breast cancer diagnosis. Statistically significant associations ($p < 5E{-}02$) are denoted with an asterisk.

[a]We performed adjusted analyses by including age at diagnosis, nodal status, size category, grade, estrogen receptor (ER) status, ERB-B2 receptor tyrosine kinase 2 (*ERBB2* [MIM: 164870]) status of the first breast cancer, (*neo*)adjuvant chemotherapy, endocrine therapy, and trastuzumab as covariates in the Cox regression model.

[b]Combined PTVs and pathogenic/likely pathogenic rare missense variants as defined in Dorling et al. (2021).[18]

Given the prior evidence that PTVs and pathogenic/likely pathogenic rare MSVs in the nine main BC-susceptibility genes increase BC risk,[18] and therefore their hypothesized impact on disease outcome through increased risk of CBC or recurrence, results of analyses were considered statistically significant at a nominal level of $p < 0.05$. For the secondary analyses of the 25 other genes, a Bonferroni corrected threshold of $0.05/25 = 0.002$ was used.

Results

Characteristics of the 34 Breast Cancer Association Consortium studies and 34,401 women included in these analyses are shown in Tables S1, S2, and S3. Over a median follow-up of 10.9 years, there were 6,898 deaths, of which 3,449 were known BC deaths.

Contralateral breast cancer risk

CBC risk analyses were based on 30,628 women with information on CBC diagnoses. Of 676 CBCs, 103 were diagnosed among carriers of variants in at least one of the nine BC-susceptibility genes, namely of PTVs in *ATM*, *BARD1*, *BRCA1*, *BRCA2*, *CHEK2*, *PALB2*, *RAD51C*, *RAD51D*, *TP53*, and/or pathogenic/likely pathogenic MSVs in *BRCA1*, *BRCA2*, and *TP53* (Table S6). HRs and 95% CIs for the association of PTVs in the nine main BC genes and of likely pathogenic rare MSVs in *BRCA1*, *BRCA2*, and *TP53* classified as pathogenic/likely pathogenic with CBC risk are shown in Table 1 and Figure 1. Only analyses adjusted by tumor characteristics, age at diagnosis of the first BC, and systemic treatment are reported in the text, unless differently specified. Carriers of combined PTVs and pathogenic/likely pathogenic MSVs in *BRCA1* had a nearly 3-fold increased CBC risk compared to non-carriers [HR (95% CI): 2.88 (1.70–4.87), p = 8.8E−05]. Carriers of combined PTVs and pathogenic/likely pathogenic MSVs in *BRCA2* had a 2-fold increased CBC risk compared to non-carriers [HR (95% CI): 2.31 (1.39–3.85), p = 1.3E−03]. The association was more evident within women diagnosed with an ER-negative for *BRCA1* and an ER-positive first BC for *BRCA2* (Tables S7 and S8), although the heterogeneity tests were not significant (Table S9). For combined PTVs and pathogenic/likely pathogenic MSVs in *TP53*, there was evidence of strong association with CBC risk although the 95% CI was wide [HR (95% CI): 8.29 (2.53–27.21), p = 5.1E−04]. The estimated unadjusted HR (95% CI) for combined PTVs and pathogenic/likely pathogenic MSVs in *BRCA1*, *BRCA2*, and *TP53* based on women diagnosed with first BC before age 40 years were 3.90 (1.52–10.02), 2.61 (1.00–6.78), and 13.15 (3.18–54.39), respectively, with no strong evidence of heterogeneity by age at first BC diagnosis ($p > 1.3E{-}01$). PTVs in *CHEK2* were associated with a 2-fold increased CBC risk compared to non-carriers, with no difference in the HR by ER status of the first BC (Table S9). The estimated HR was higher for *CHEK2* c.1100delC [HR (95% CI): 2.43 (1.63–3.62), p = 1.5E−05] than for other *CHEK2* PTVs, in aggregate [HR (95% CI): 1.40 (0.49–3.96)], but the difference in HR was not statistically significant. There was evidence that rare MSVs in *CHEK2*, in aggregate, were also associated with an increased risk of CBC [HR (95% CI): 1.78 (1.08–2.94); Table S10], with no evidence of differential association by ER status of the first BC (Tables S11–S13). The estimated adjusted HR (95% CI) for PTVs in *PALB2* was

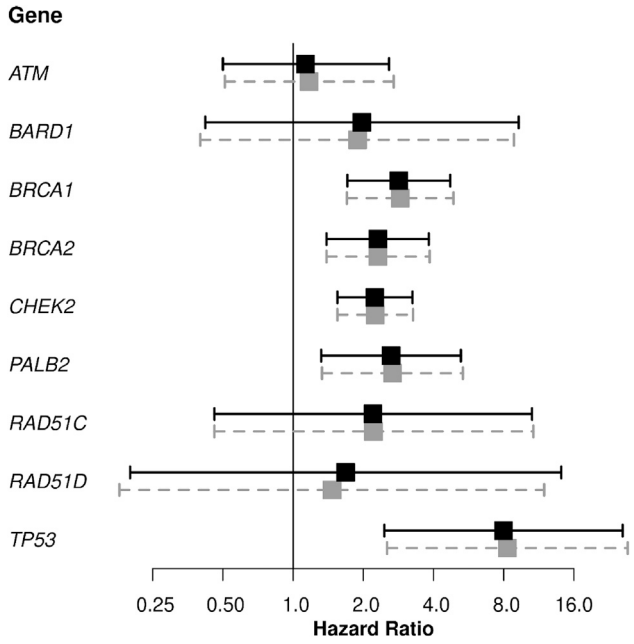

Figure 1. Forest plot showing the association of protein-truncating variants (PTVs) in *ATM*, *BARD1*, *CHEK2*, *PALB2*, *RAD51C*, and *RAD51D* and of combined PTVs and pathogenic/likely pathogenic rare missense variants (MSVs) in *BRCA1*, *BRCA2*, and *TP53* with contralateral breast cancer (CBC) risk

The black squares and solid lines represent hazard ratio (HR) estimates and 95% confidence intervals (CIs) from the unadjusted analyses, respectively. The gray squares and dashed gray lines represent HR estimates and 95% CIs from the adjusted analyses. We performed the adjusted analyses by including age at diagnosis, nodal status, size category, grade, estrogen receptor (ER) status, ERB-B2 receptor tyrosine kinase 2 (*ERBB2*) status of the first breast cancer, (*neo*)adjuvant chemotherapy, endocrine therapy, and trastuzumab as covariates in the Cox regression model. For each gene, the exact numbers of women and CBCs are reported in Table 1. PTVs and pathogenic/likely pathogenic MSVs were defined as in Dorling et al.[18]

2.67 (1.33–5.35) (Table 1). PTVs in *ATM*, *BARD1*, *RAD51C*, and *RAD51D* were not statistically significantly associated with CBC risk (Table 1); however, the confidence intervals for HRs in each case included 2, a suggested threshold to define pathogenic/likely pathogenic variants that "could be used to inform medical management."[27]

Results of sensitivity analyses comparing with women who did not carry PTVs in any of the nine main BC-susceptibility genes nor likely pathogenic MSVs in *BRCA1*, *BRCA2*, and *TP53* were consistent with the main analyses (Tables S14 and S15). Sensitivity analyses restricted to cohort, population-based, and hospital-based studies were also consistent (Tables S16 and S17).

The estimated 10-year cumulative incidence of CBC, after allowing for the competing risk of death from any cause, was 7.2% for carriers of PTVs and pathogenic/likely pathogenic MSVs in *BRCA1*, 5.4% for carriers of PTVs and pathogenic/likely pathogenic MSVs in *BRCA2*, 6.7% for PTVs carriers in *CHEK2*, 5.4% in PTVs carriers in *PALB2*, and 18.0% in carriers of PTVs and pathogenic/likely pathogenic MSVs combined in *TP53* (Figure 2).

Among the remaining 25 putative BC-susceptibility genes, there was evidence for association of PTVs in *RAD50* (MIM: 604040) [HR (95% CI): 4.75 (1.86–12.15), p = 1.2E−03; Table S18] and MSVs in *XRCC2* (MIM: 600375) with CBC risk [HR (95% CI): 4.05 (1.88–8.73), p = 3.8E−04; Table S19], with no evidence of differential association by ER status of the first BC (Tables S20–S25).

Breast cancer-specific survival

HRs for association of PTVs in *ATM*, *BARD1*, *CHEK2*, *PALB2*, *RAD51C*, and *RAD51D* and of combined PTVs and pathogenic/likely pathogenic MSVs in *BRCA1*, *BRCA2*, and *TP53* with BCSS are shown in Table 2 and Figure 3. There was a statistically significant association of combined PTVs and pathogenic/likely pathogenic MSVs in *BRCA2* with decreased BCSS in the unadjusted analysis. However, after adjusting for tumor characteristics, age at diagnosis, and systemic treatment given for the first BC, the HR was no longer statistically significant [HR (95% CI): 1.20 (0.95–1.52), p = 1.2E−01]. HRs differed by ER status of the first BC [HR (95% CI): 1.53 (1.13–2.07) and 0.76 (0.44–1.31), for ER-positive and ER-negative first BC, respectively; $p_{heterogeneity}$ = 2.2E−02; Tables S9, S26, and S27]. PTVs in *CHEK2* were associated with higher risk of BC death [HR (95% CI): 1.39 (1.13–1.72), p = 2.2E−03] with no strong evidence of heterogeneity in HRs by ER status (Table S9). There was also weak evidence for a poorer BCSS for carriers of rare MSVs in *CHEK2* [HR (95% CI): 1.23 (0.97–1.57); Table S28], with no evidence of differential association by ER status of the first BC (Tables S13, S29, and S30). PTVs in *PALB2* were associated with poorer BCSS (unadjusted HR = 1.65), but this association was attenuated after adjusting for additional tumor characteristics [HR (95% CI): 1.39 (0.98–1.98), p = 6.8E−02]. There was no evidence for an association between PTVs in *ATM*, *BARD1*, *BRCA1*, *RAD51C*, and *RAD51D* and likely pathogenic MSVs in *BRCA1* and BCSS. For *TP53* there was weak evidence for poorer BCSS in carriers of combined PTVs and pathogenic/likely pathogenic MSVs [HR (95% CI): 2.08 (0.95–4.57), p = 6.8E−02] and of all rare MSVs in aggregate [HR (95% CI): 1.63 (1.11–2.38), p = 1.2E−02; Table S28]. Sensitivity analyses restricted to cohort, population-based, and hospital-based studies were consistent with the main analyses (Tables S31 and S32).

Of the remaining 25 putative BC-susceptibility genes evaluated, PTVs in *BABAM2* (MIM: 610497) were associated with decreased BCSS [Table S33: HR (95% CI): 7.74 (1.67–35.84), p = 8.8E−03], while PTVs in *GEN1* (MIM: 612449) and *BRIP1* (MIM: 605882) were associated with decreased BCSS in ER-negative tumors [Tables S34 and S35; HR (95% CI): 7.41 (1.99–27.66) and 4.97 (1.42–17.43) for *GEN1* and *BRIP1*, respectively]. However, these associations were not statistically significant after Bonferroni correction for 25 tests. MSVs, in aggregate, in the 25 putative BC genes were not associated with BCSS (Tables S36–S38). For genes with evidence of association of PTVs or MSVs with both CBC risk and BCSS, results of the BCSS analyses censored for CBC were broadly similar (Tables S39 and S40).

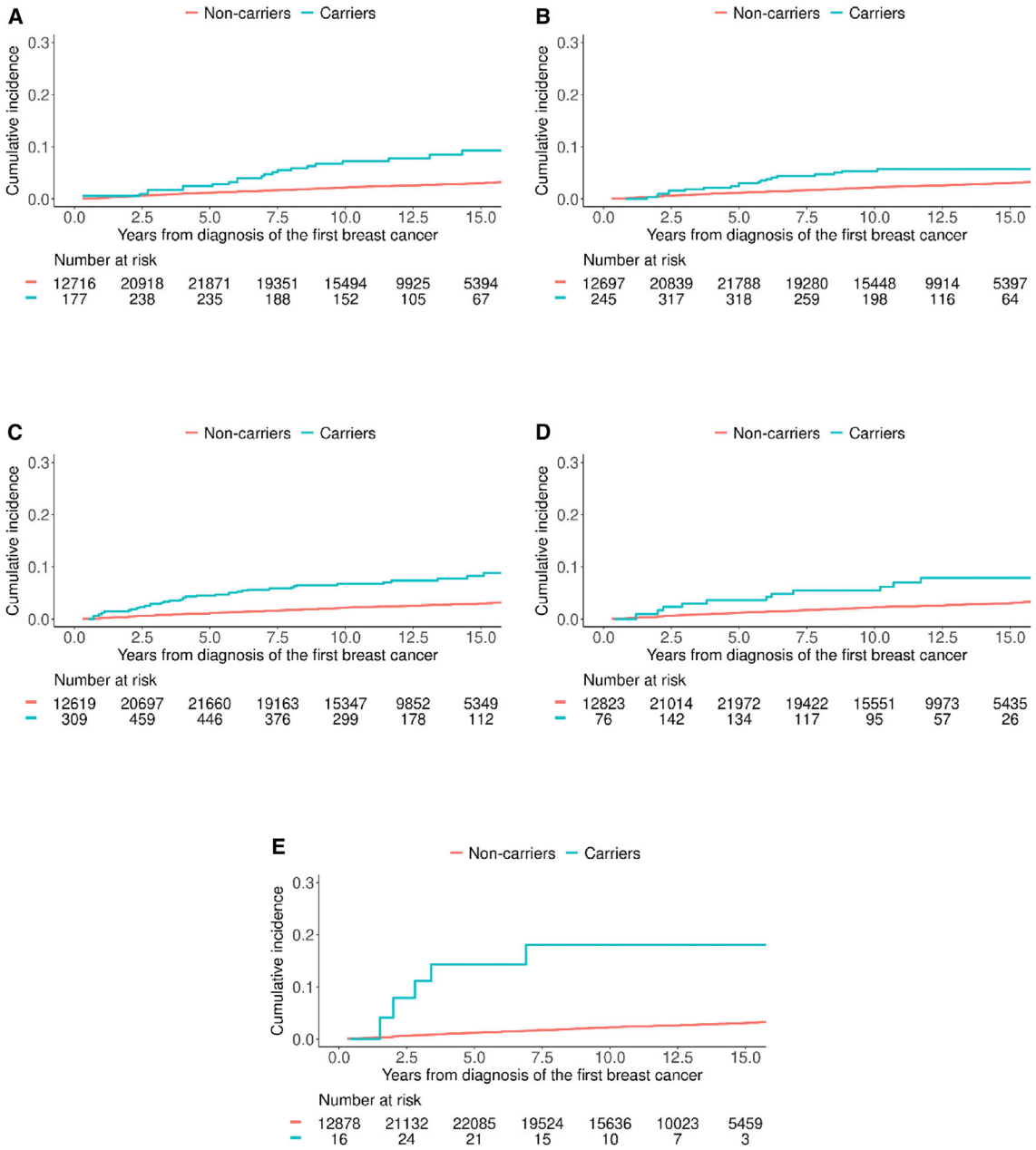

Figure 2. Cumulative incidence curves for developing contralateral breast cancer in the presence of competing risk of death for any cause

(A–E) Cumulative incidence for carriers (blue line) and non-carriers (red line) of combined protein-truncating variants (PTVs) and pathogenic/likely pathogenic missense variants (MSVs) in *BRCA1* (A), combined PTVs and pathogenic/likely MSVs in *BRCA2* (B), PTVs in *CHEK2* (C), PTVs in *PALB2* (D), and combined PTVs and pathogenic/likely pathogenic MSVs in *TP53* (E). PTVs and pathogenic/likely pathogenic MSVs as defined in Dorling et al.[18] were considered. We limited the y axis to the range (0.00, 0.30) to better visualize the curves. The x axis is restricted to 15 years from diagnosis because of the low number of carriers after 15 years.

Overall survival

Results of overall survival analyses are shown in Tables S41 and S42. Combined PTVs and pathogenic/likely pathogenic MSVs in *BRCA2* and PTVs in *CHEK2* were associated with poorer overall survival, though the HRs were smaller than for BCSS [Table S41; HRs (95% CIs): 1.27 (1.06–1.52), p = 1.1E−02 and 1.21 (1.03–1.43), p = 2.0E−02, for *BRCA2* and *CHEK2*, respectively]. In *TP53*, combined PTVs and pathogenic/likely pathogenic MSVs were significantly associated with poorer overall survival [HR (95% CI): 3.47 (1.98–6.09), p = 1.5E−05].

Discussion

Using data from the BRIDGES[18] study, we evaluated PTVs and rare MSVs in nine confirmed (*ATM*, *BARD1*, *BRCA1*,

Table 2. Association of protein-truncating variants in nine breast cancer genes and of pathogenic/likely pathogenic rare missense variants in *BRCA1*, *BRCA2*, and *TP53* with breast cancer-specific survival

Gene	Unadjusted analyses		Adjusted analyses[a]		No. of women		No. of BC deaths	
PTVs (unless indicated otherwise)	HR (95% CI)	p	HR (95% CI)	p	Non-carriers	Carriers	Non-carriers	Carriers
ATM	1.24 (0.85–1.83)	2.7E−01	1.07 (0.73–1.57)	7.3E−01	34,151	250	3,421	28
BARD1	1.14 (0.46–2.79)	7.8E−01	0.90 (0.38–2.15)	8.2E−01	34,347	54	3,444	5
BRCA1[b]	1.22 (0.89–1.66)	2.2E−01	0.90 (0.66–1.22)	4.9E−01	34,037	364	3,406	43
BRCA2[b]	1.54 (1.21–1.95)*	5.0E−04*	1.20 (0.95–1.52)	1.2E−01	33,914	487	3,372	77
CHEK2	1.47 (1.19–1.82)*	3.7E−04*	1.39 (1.13–1.72)*	2.2E−03*	33,702	699	3,349	100
c.1100delC	1.46 (1.15–1.85)*	1.6E−03*	1.43 (1.13–1.81)*	3.0E−03*	33,702	561	3,349	81
Other	1.51 (0.93–2.44)	9.6E−02	1.26 (0.79–2.02)	3.4E−01	33,702	138	3,349	19
PALB2	1.65 (1.15–2.36)*	6.7E−03*	1.39 (0.98–1.98)	6.8E−02	34,177	224	3,414	35
RAD51C	0.77 (0.26–2.28)	6.4E−01	0.79 (0.27–2.38)	6.8E−01	34,361	40	3,446	3
RAD51D	1.48 (0.63–3.46)	3.7E−01	0.95 (0.43–2.12)	9.1E−01	34,370	31	3,443	6
TP53[b]	2.52 (1.13–5.60)*	2.4E−02*	2.08 (0.95–4.57)	6.8E−02	34,354	47	3,441	8

Abbreviations: No., number; BC, breast cancer; PTVs, protein-truncating variants; HR, hazard ratio; CI, confidence interval; p, p value. Analyses included women from 34 studies listed in Table S1, excluding women who developed a CBC before study entry. Statistically significant associations ($p < 5E{-}02$) are denoted with an asterisk.
[a]We performed adjusted analyses by including age at diagnosis, nodal status, size category, grade, estrogen receptor (ER) status ERB-B2 receptor tyrosine kinase 2 (*ERBB2*) status of the first breast cancer, (*neo*)adjuvant chemotherapy, endocrine therapy, and trastuzumab as covariates in the Cox regression model.
[b]Combined PTVs and pathogenic/likely pathogenic rare missense variants as defined in Dorling et al. (2021).[18]

BRCA2, *CHEK2*, *PALB2*, *RAD51C*, *RAD51D*, *TP53*) and 25 putative BC-susceptibility genes[18] for association with CBC risk and BCSS both overall and by ER status of the first BC.

Combined PTVs and pathogenic/likely pathogenic MSVs in *BRCA1*, *BRCA2*, and *TP53* and PTVs in *CHEK2* and *PALB2* were associated with increased CBC risk. These findings are consistent with recent studies[18,28,29] and support the general hypothesis that mutations that predispose to a first BC also predispose to a second BC. Carriers of PTVs and pathogenic/likely pathogenic MSVs in *BRCA1* and *BRCA2* had approximately a 2- and 3-fold increased CBC risk, respectively, as reported previously.[25,30] The larger HR estimates in women with an ER-negative first BC for *BRCA1* and in women with ER-positive first BC for *BRCA2* probably reflect the fact that *BRCA1* and *BRCA2* mutation carriers are most likely to develop ER-negative and ER-positive first BCs, respectively.[31] *BRCA1* carriers with ER-positive first BC and *BRCA2* carriers with ER-negative first BC did not appear to have an increased risk of CBC. However, in both cases there was no evidence of heterogeneity of the HR estimates by ER status of the first BC; therefore, we cannot conclude that surveillance or risk-reduction strategies in *BRCA1* and *BRCA2* carriers should differ according to the ER status of the first BC. PTVs in *PALB2* were associated with an over 2.5-fold increased CBC risk. HRs for *BRCA1*, *BRCA2*, and *PALB2*, while clearly elevated, were lower than the relative risk estimates for the first BC. PTVs in *CHEK2* were associated with an over 2-fold increased CBC risk, similar to the relative risk for the first BC reported in BRIDGES,[18] and to a previous CBC analysis.[5] In *TP53*, PTVs and pathogenic/likely pathogenic MSVs combined were associated with an 8-fold increased CBC risk, consistent with the results of a previous study focused on carriers younger than age 36 years at diagnosis of the first BC[26] and four times higher than the corresponding risk of first BC,[18] although this estimate is imprecise because of the low numbers of carriers.

The similarity of the relative risk estimates for a first BC and a CBC for *CHEK2* PTVs are broadly consistent with a model in which the risks of the second cancer are independent of the first, given the individual's genotype.[32] *CHEK2* MSVs are also associated in aggregate with BC risk,[18] and the increased CBC risk in *CHEK2* MSV carriers, although lower than for PTV carriers, is also consistent with this model. On the other hand, the lower relative risks of CBC (in comparison with the first BC) observed for carriers of rare PTVs in *PALB2* and of rare PTVs and pathogenic/likely pathogenic MSVs in *BRCA1* and *BRCA2* could be partly explained by the fact that carriers of high-risk variants[20] diagnosed with cancer are more depleted for other risk factors (particularly risk alleles in common susceptibility variants)—a phenomenon known as elimination of susceptibles, or index event bias.[33,34] However, other factors, for example differential effects in carriers of endocrine and/or chemotherapy regimens that have been shown to lower CBC risk,[35] may also play a role. An additional explanation for the observed lower CBC HR estimates compared to the estimates for the first BC, and lower estimated CBC incidence in carriers of PTVs and/or pathogenic/likely pathogenic rare MSVs in *BRCA1* and *BRCA2* than what has been previously reported,[25,36–38] is that some women in our study sample may have undergone prophylactic contralateral mastectomy. Contralateral mastectomy virtually eliminates the risk of developing a CBC, which in turn

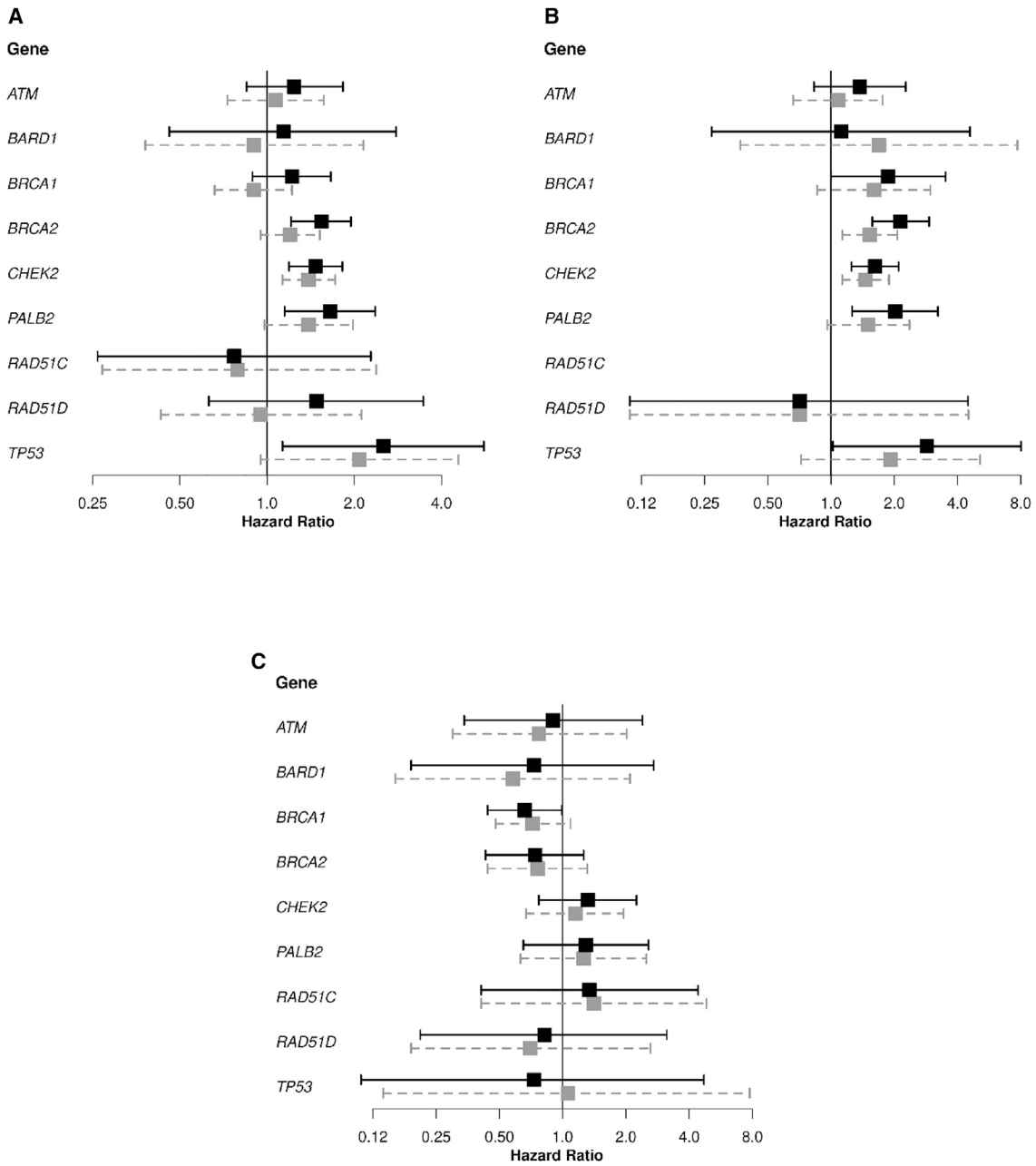

Figure 3. Forest plots showing the association of PTVs in *ATM*, *BARD1*, *CHEK2*, *PALB2*, *RAD51C*, and *RAD51D* and of combined PTVs and pathogenic/likely pathogenic rare missense variants (MSVs) in *BRCA1*, *BRCA2*, and *TP53*, with breast cancer-specific survival, in women from all studies, excluding women who developed a CBC before study entry

(A–C) The results of the analysis shown in Table 2 are shown in (A). The results of the analysis based on women diagnosed with an estrogen receptor (ER)-positive first breast cancer (Table S26) are shown in (B). The hazard ratios (HRs) for the association of PTVs in *RAD51C* with breast cancer-specific survival could not be estimated because of the low number of carriers and the absence of carriers who died of breast cancer (Table S26). The results of the analysis based on women diagnosed with an estrogen ER-negative first breast cancer (Table S27) are shown in (C). The black squares and solid lines represent hazard ratio (HR) estimates and 95% confidence intervals (CIs) from the unadjusted analyses, respectively. The gray squares and dashed gray lines represent HR estimates and 95% CIs from the adjusted analyses. Adjusted analyses shown in (A) included age at diagnosis, nodal status, size category, grade, ER status, ERB-B2 receptor tyrosine kinase 2 (*ERBB2*) status of the first breast cancer, (*neo*)adjuvant chemotherapy, endocrine therapy, and trastuzumab as covariates in the Cox regression model. Adjusted analyses in (B) and (C) included the same covariates as in (A) except the ER status of the first breast cancer. PTVs and pathogenic/likely pathogenic MSVs were defined as in Dorling et al.[18]

might affect BCSS because CBC occurrence is associated with poorer prognosis.[9–11,13] This would result in lower HR (for both CBC risk and BCSS) and CBC incidence estimates: the downward bias is stronger as the proportion of women undergoing contralateral mastectomy increases. Unfortunately, we did not have information on contralateral mastectomy and thus could not account for it in the analyses; therefore, the HR could be a lower bound to the

true estimate. On the other hand, within our study population, genetic testing was mostly carried out in the research setting (BRIDGES panel) retrospectively (long) after women were diagnosed and treated. Therefore, most of the women included in the analyses would not have been aware that they carried pathogenic variants in *BRCA1/2* and *TP53*, either before or at the time of diagnosis. Moreover, most of study individuals are part of population- and hospital-based studies and without family history. This could also partly explain the lower CBC incidence in *BRCA1* and *BRCA2* carriers compared with previous reports.[25,36–38] Assuming that mainly women known to be carriers of pathogenic variants in either *BRCA1/2* or *TP53* or women with known family history (from family or clinical genetic center-based studies) underwent a contralateral mastectomy, these would be a minor part of our study population and we do not expect their inclusion to substantially affect the results. Although the past decade has seen an increase in the number of women opting for a contralateral mastectomy without knowing their mutation status,[39–42] to the best of our knowledge most of this increase has been in North America. Most of our study population comes from European countries and only includes two USA studies and one study from Canada, which amounts to approximately 7% of the total study population. Again, it is unlikely that inclusion of this small percentage would substantially affect the results.

PTVs in *ATM*, *BARD1*, *RAD51C*, and *RAD51D* were not associated with statistically significantly increased CBC risk; however, HRs estimates were >1 in each case, confidence limits were wide, and the HRs were mostly consistent with the relative risk estimates for a first BC. An earlier study also reported no significantly elevated risk for pathogenic/likely pathogenic variants in *ATM*.[43]

Risk of BC-specific death was increased in carriers of PTVs in *CHEK2* and *PALB2*, and of PTVs/MSVs in *BRCA2* and *TP53*; these associations were not substantially altered by censoring for CBC. For *BRCA2*, the stronger increase in risk of BC death observed in women with an ER-positive BC compared to women with an ER-negative BC is consistent with the results of a previous study.[44] The association with BCSS of *BRCA2* PTVs and pathogenic/likely pathogenic MSVs in women with ER-positive cancers, and of *CHEK2* PTVs and *TP53* MSVs in overall BC, although attenuated, remained significant after adjusting for age at diagnosis and tumor characteristics, suggesting that part of the effect is not explained by less favorable tumor characteristics or systemic treatment given for the first BC. The observed association between PTV carriers in *PALB2* and BCSS was attenuated and not statistically significant in the adjusted analyses, suggesting that most of the effect might be mediated by tumor characteristics or treatment. Consistent with the fact that PTVs/MSVs in *TP53* are associated with a spectrum of cancers, the HR for association with overall survival was larger than for BCSS. Interestingly, PTVs and pathogenic/likely pathogenic rare MSVs in *BRCA1* were not associated with BCSS, in spite of the fact that *BRCA1* carriers are more likely to develop ER-negative tumors,[31] which are known to lead to a higher risk of short term recurrence and mortality.[45] This lack of association might still be due to chance, since the upper 95% confidence limit on the unadjusted HR (1.66) is still consistent with an important survival difference. We speculate that the lack of association of PTVs and pathogenic/likely pathogenic rare MSVs in *BRCA1* with BCSS in our study might be explained by the fact that *BRCA1* carriers have a better response to systemic treatment for the first BC, in particular chemotherapy.[46]

Analyses of the 25 remaining putative BC-susceptibility genes showed some evidence of association between CBC risk, PTVs in *RAD50*, and MSVs in *XRCC2* and between BCSS and PTVs in *BABAM2* (in BC overall), *GEN1*, and *BRIP1* (ER-negative subtype), although the latter three analyses had limited power and Bonferroni-corrected p values for 25 tests were not statistically significant. A potential role of *XRCC2* polymorphisms[47] and germline PTVs in *RAD50*[48] in BC prognosis have been reported. Previous evidence supporting a role of germline PTVs or rare MSVs in *BABAM2* and *GEN1* in BC prognosis is lacking, while PTVs/potentially damaging rare MSVs in *BRIP1* have been reported to be associated with ovarian cancer (MIM: 167000),[49] which could explain the observed poorer survival of carriers in our study.

The main strength of this study is its large sample size and long follow-up, which allowed us to provide estimates for the association between PTVs and rare MSVs in BC-susceptibility genes with CBC risk and BCSS by gene. This is relevant because data on prognosis for individual genes apart from *BRCA1*, *BRCA2*, and *CHEK2* have been limited. The inclusion of studies that selected women with family history of BC improved power but could bias the association estimates. However, sensitivity analyses restricted to women without family history of BC yielded results in line with those from the main analyses. As previously mentioned, most of the studies included in our study sample were either population- or hospital-based and therefore most women did not have family history. Some genes, such as *TP53*, are related to rare multi-cancer syndromes and usually detected at genetic centers and excluded from population-based studies, making unbiased estimation difficult. Another limitation was the fact that for 22% of the deaths observed during follow-up, cause of death was unknown, reducing the power to detect associations with BCSS. Similarly, CBC information may have been incomplete for some studies, and therefore some of our estimates might be slightly underestimated. Despite the large sample size, variants in some of the genes are so rare that their association with CBC risk and survival could not be estimated. The statistical power to detect significant interactions by ER status and age at diagnosis of the first BC was also limited. Moreover, there was insufficient data to carry out analyses based on tumor characteristics of the CBC. Finally, only women of European ancestry were included in the analyses. Larger studies, including those drawing upon women with different ethnicities, are necessary to provide

precise and reliable estimates of CBC and BCSS in populations worldwide.

In conclusion, PTVs and/or rare pathogenic/likely pathogenic MSVs in five BC-susceptibility genes (*BRCA1*, *BRCA2*, *CHEK2*, *PALB2*, and *TP53*) are associated with increased CBC risk; PTVs and/or rare pathogenic/likely pathogenic MSVs in three of these genes (*BRCA2*, *CHEK2*, and *TP53*) are associated with poorer BCSS, not completely explained by the increased CBC risk, tumor characteristics, or treatment. There is limited evidence of associations for other putative BC-susceptibility genes. Our results have the potential to improve BC-risk counseling, prognostic estimates, and prediction models for BC outcome. In particular, the CBC findings are relevant to improve treatment, follow-up, and screening of women diagnosed with BC.

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Supplemental information

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Conception and design: A.M., N.M., T.A.M., H.N., P.D., D.F.E., and M.K.S. Administrative support: M.K.B., J.W., and R.K. Provision of study materials or patients: all authors. Collection and assembly of data: all authors. Data analysis and interpretation: A.M., N.M., T.A.M., H.N., P.D., D.F.E., and M.K.S. Manuscript writing: all authors; initial draft: A.M. and M.K.S.; final approval of manuscript: all authors.

Declaration of interests

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Supplemental information

The impact of coding germline variants on contralateral breast cancer risk and survival

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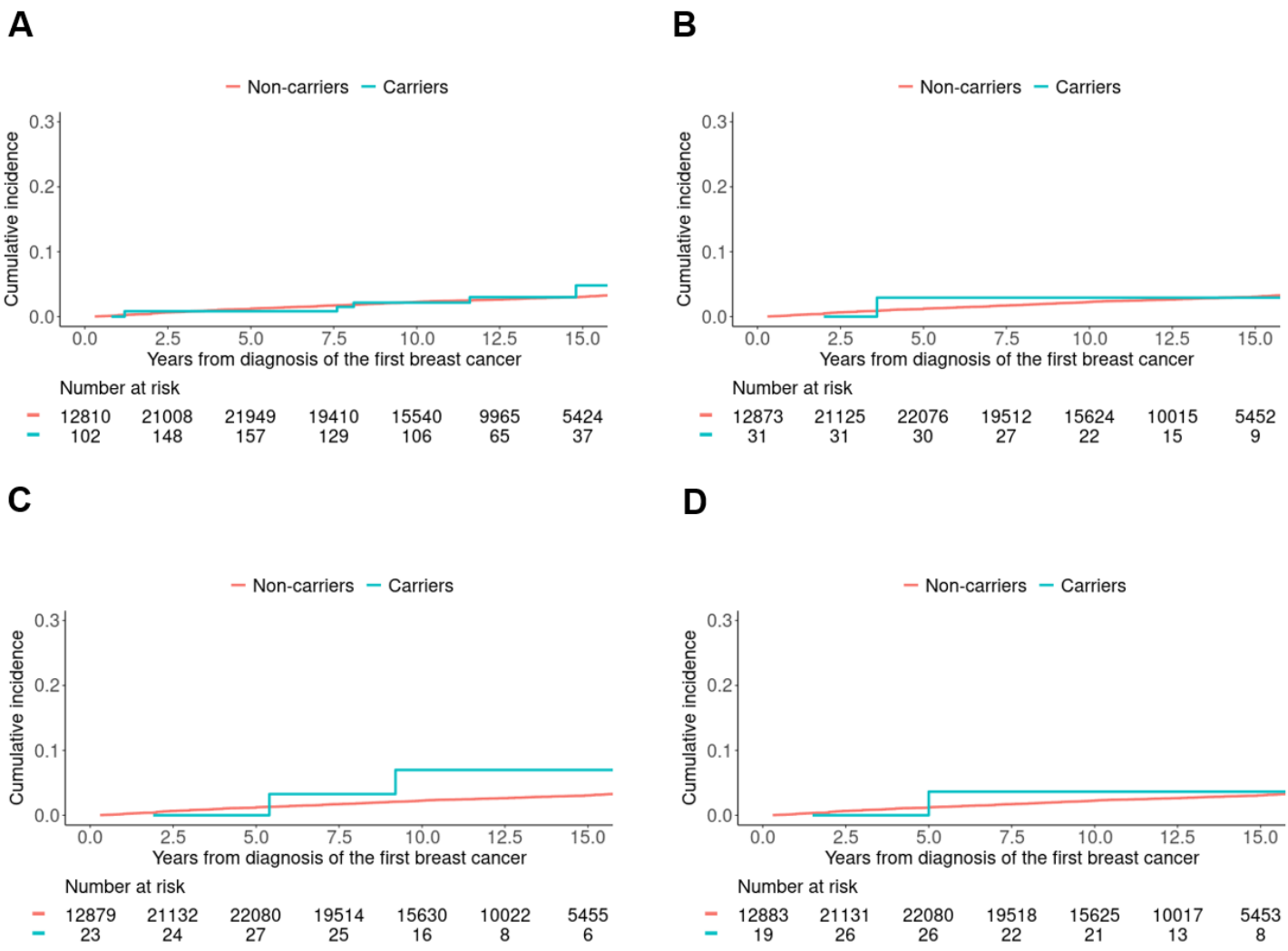

Figure S1. Cumulative incidence curves of contralateral breast cancer occurrence in the presence of competing risk of death for any cause.

Cumulative incidence for carriers (blue line) and non-carriers (red line) of: protein-truncating variants (PTVs) in *ATM* (panel A), PTVs in *BARD1* (panel B), PTVs in *RAD51C* (panel C), PTVs in *RAD51D* (panel D). PTVs as in Dorling et al. (NEJM, 2021) were considered. The y-axis is limited to the range (0.00,0.30) to better visualize the curves. The x-axis is restricted to 15 years from diagnosis due to the low number of carriers after 15 years follow-up.

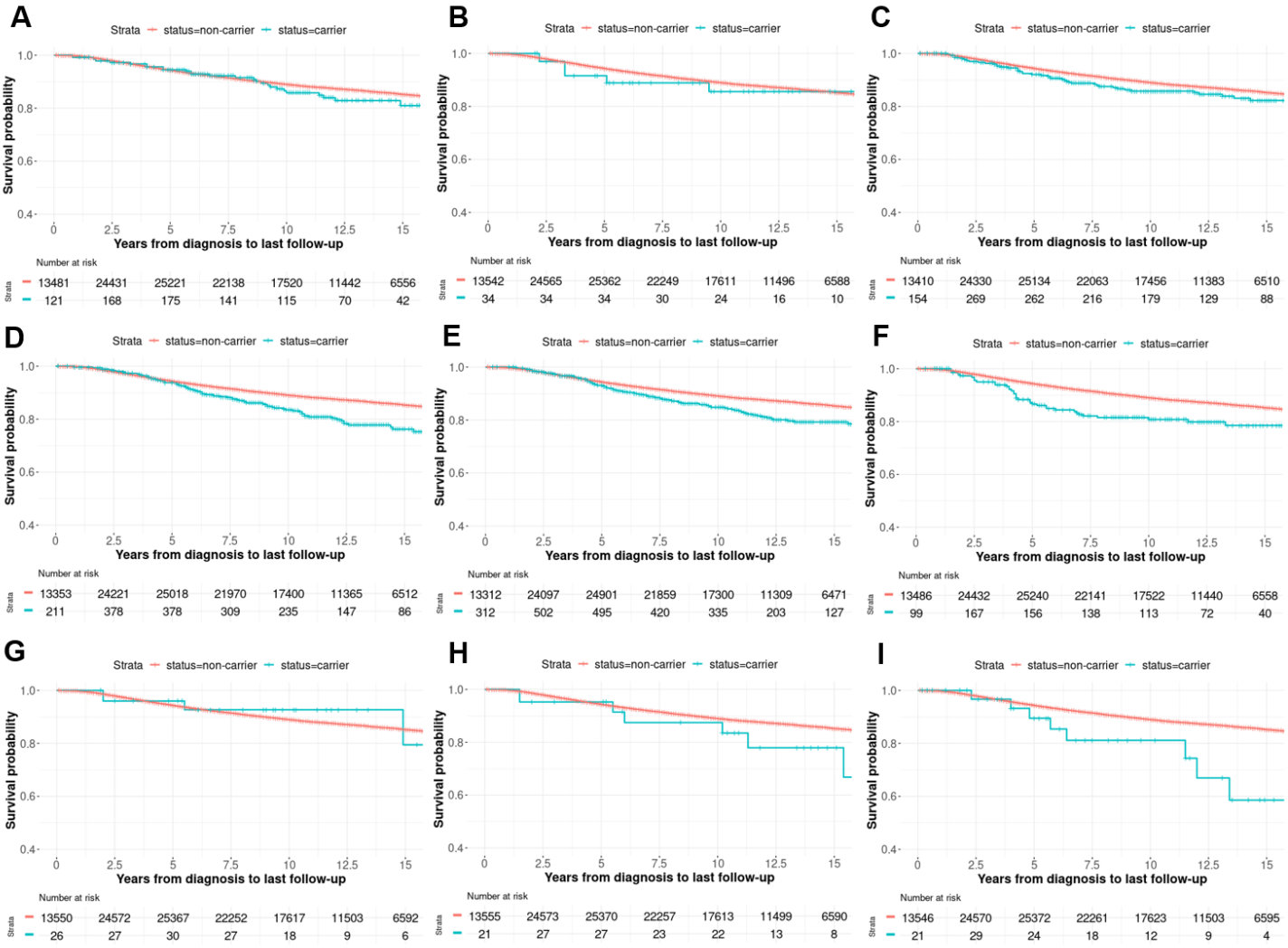

Figure S2. **Kaplan-Meier plots of breast cancer-specific survival**.

Kaplan-Meier plots for carriers (blue line) and non-carriers (red line) of: protein-truncating variants (PTVs) in *ATM* (panel A), PTVs in *BARD1* (panel B), combined PTVs and pathogenic/likely pathogenic missense variants (MSVs) in *BRCA1* (panel C), combined PTVs and pathogenic/likely pathogenic MSVs in *BRCA2* (panel D), PTVs in *CHEK2* (panel E), PTVs in *PALB2* (panel F), PTVs in *RAD51C* (panel G), PTVs in *RAD51D* (panel H), combined PTVs and pathogenic/likely MSVs in *TP53* (panel I). Pathogenic/likely pathogenic MSVs as defined in Dorling et al. (NEJM, 2021) were considered. The y-axis is limited to the range (0.4,1.0) to better visualize the curves. The x-axis is restricted to 15 years from diagnosis due to the low number of carriers after 15 years follow-up.

Table S2. Characteristics of the study sample and breast tumors, overall and by ER status of the first breast cancer, excluding women who developed a contralateral breast cancer before study entry.

	All	ER-positive first BC	ER-negative first BC
Number of women	34401	22590	5665
Number of all-cause deaths	6898	4207	1467
Number of breast cancer-specific deaths	3449	1997	834
Number of contralateral breast cancers	692	433	139
Age at CBC diagnosis, median (IQR)	60 (52-70)	60 (52-69)	57 (47-67)
Characteristics of the first BC			
Age at diagnosis, median (IQR)	56 (48-64)	57 (49-65)	54 (45-62)
Year of diagnosis, median (IQR)	2003 (1999-2006)	2003 (2000-2006)	2002 (1999-2005)
Missing, n	447	304	91
Nodal status, n (%)			
Negative	18292 (63.7)	13029 (63.7)	3065 (60.5)
Positive	10441 (36.3)	7434 (36.3)	2002 (39.5)
Missing, n	5668	2127	598
Tumor size, n (%)			
≤2cm	17306 (65.5)	12661 (67.6)	2405 (53.1)
>2cm and ≤5cm	8261 (31.2)	5535 (29.5)	1893 (41.8)
>5cm	870 (3.3)	535 (2.9)	232 (5.1)
Missing, n	7964	3859	1135
Tumor grade, n (%)			
1	5667 (20.1)	4749 (23.7)	234 (4.7)
2	13919 (49.5)	11024 (55.0)	1407 (28.4)
3	8556 (30.4)	4259 (21.3)	3321 (66.9)
Missing, n	6259	2558	703
ER status, n (%)			
Negative	5665 (20.0)	-	5665 (100.0)
Positive	22590 (80.0)	22590 (100.0)	-
Missing, n	6146	-	-
PR status, n (%)			
Negative	7886 (32.7)	3483 (18.3)	4376 (86.1)
Positive	16261 (67.3)	15523 (81.7)	707 (13.9)
Missing	10254	3584	582
***ERBB2* status**, n (%)			
Negative	15234 (82.7)	12515 (86.0)	2589 (69.8)
Positive	3185 (17.3)	2041 (14.0)	1122 (30.2)
Missing, n	15982	8034	1954
Surgery, n (%)			
No surgery	548 (2.2)	189 (1.2)	49 (1.2)
Breast saving	8391 (34.3)	6338 (38.8)	1522 (35.9)
Mastectomy (with or without axillary)	6379 (26.1)	4185 (25.6)	1461 (34.5)
Type unknown	9122 (37.3)	5639 (34.5)	1206 (28.5)
Missing, n	9961	6239	1427
Radiation, n (%)			
No radiation	6544 (26.3)	3947 (23.6)	1091 (25.9)
Breast	6991 (28.1)	5310 (31.8)	1225 (29.1)
Breast and lymph nodes	2016 (8.1)	1443 (8.6)	476 (11.3)
Lymph nodes only	318 (1.3)	256 (1.5)	50 (1.2)
Organ unknown	8980 (36.1)	5747 (34.4)	1374 (32.6)
Missing, n	9552	5887	1449
Neoadjuvant chemotherapy, n (%)			
No	20061 (93.9)	13487 (95.0)	3339 (89.2)
Yes	1302 (6.1)	713 (5.0)	406 (10.8)
Missing, n	13038	8390	1920
Adjuvant chemotherapy, n (%)			
No	14785 (61.9)	10485 (65.1)	1493 (36.2)
Yes	9111 (38.1)	5629 (34.9)	2628 (63.8)
Missing, n	10505	6476	1544
Endocrine therapy, n (%)			
No	7454 (30.7)	2963 (18.0)	2983 (73.9)
Yes	16795 (69.3)	13454 (82.0)	1053 (26.1)
Missing, n	10152	6173	1629
Trastuzumab, n (%)			
No	13866 (96.1)	8760 (96.3)	2548 (92.0)
Yes	566 (3.9)	337 (3.7)	221 (8.0)

Missing, n	19969	13493	2896

Abbreviations: BC = breast cancer; CBC = contralateral breast cancer; IQR = interquartile range; ER = estrogen receptor; PR = progesterone receptor: *ERBB2* = ERB-B2 receptor tyrosine kinase 2. Percentages are given within women with no missing values.

Table S3. Characteristics of protein-truncating variants carriers in 9 breast cancer genes and pathogenic/likely pathogenic rare missense variants carriers in *BRCA1*, *BRCA2* and *TP53* out of the study sample of 34401 women as specified in Table S2.

	***ATM* PTVs carriers**	***BARD1* PTVs carriers**	***BRCA1* carriers (PTVs + P/LP MSVs)**	***BRCA2* carriers (PTVs + P/LP MSVs)**	***CHEK2* PTVs carriers**	***PALB2* PTVs carriers**	***RAD51C* PTVs carriers**	***RAD51D* PTVs carriers**	***TP53* carriers (PTVs + P/LP MSVs)**
Women, n	250	54	364	487	699	224	40	31	47
All-cause deaths, n	56	14	88	129	163	56	8	9	18
Breast cancer-specific deaths, n	28	5	43	77	100	35	3	6	8
Contralateral breast cancers, n	6	2	21	20	39	11	2	1	6
Age at CBC diagnosis, median (IQR)	59 (52-65)	59 (57-61)	49 (43-54)	53 (41-57)	55 (46-70)	57 (49-63)	56 (56-56)	53 (53-53)	37 (30-39)
Characteristics of the first BC									
Age at diagnosis, median (IQR)	54 (46-62)	53(44-60)	45 (38-53)	50 (42-59)	53 (44-61)	52 (44-61)	57(49-63)	54 (49-62)	42 (32-57)
Year of diagnosis, median (IQR)	2003 (1999-2006)	2001 (1998-2005)	2002 (1999-2006)	2003 (1999-2006)	2002 (1998-2006)	2002 (2000-2005)	2003 (1999-2006)	2002 (1998-2005)	2002 (1999-2007)
Missing, n	1	0	8	10	13	4	1	0	0
Nodal status, n (%)									
Negative	115 (56.7)	29 (60.4)	188 (62.0)	200 (52.1)	340 (56.7)	106 (55.5)	20 (58.8)	12 (50.0)	23 (54.8)
Positive	88 (43.3)	19 (39.6)	115 (38.0)	184 (47.9)	260 (43.3)	85 (44.5)	14 (41.2)	12 (50.0)	19 (45.2)
Missing, n	47	6	61	103	99	33	6	7	5
Tumor size, n (%)									
≤2cm	117 (65.0)	28 (66.7)	165 (60.0)	211 (57.7)	332 (61.5)	100 (56.2)	16 (53.3)	13 (59.1)	19 (65.5)
>2cm and ≤5cm	55 (30.6)	12 (28.6)	97 (35.3)	132 (36.1)	188 (34.8)	71 (39.9)	13 (43.3)	6 (27.3)	8 (27.6)
>5cm	8 (4.4)	2 (4.8)	13 (4.7)	23 (6.3)	20 (3.7)	7 (3.9)	1 (3.3)	3 (13.6)	2 (6.9)
Missing, n	70	12	89	121	159	46	10	9	18
Tumor grade, n (%)									
1	22 (11.1)	8 (17.8)	12 (4.0)	26 (6.4)	89 (16.1)	13 (6.8)	8 (23.5)	2 (7.1)	2 (5.3)
2	90 (45.5)	16 (35.6)	65 (21.9)	192 (47.2)	312 (56.3)	90 (46.9)	11 (32.4)	9 (32.1)	18 (47.4)
3	86 (43.4)	21 (46.7)	220 (74.1)	189 (46.4)	153 (27.6)	89 (46.4)	15 (44.1)	17 (60.7)	18 (47.4)
Missing, n	52	9	67	80	145	32	6	3	9
ER status, n (%)									
Negative	23 (12.5)	21 (47.7)	218 (71.9)	99 (25.4)	76 (13.2)	48 (26.7)	12 (38.7)	11 (47.8)	10 (24.4)
Positive	161 (87.5)	23 (52.3)	85 (28.1)	291 (74.6)	501 (86.8)	132 (73.3)	19 (61.3)	12 (52.2)	31 (75.6)
Missing, n	66	10	61	97	122	44	9	8	6
PR status, n (%)									
Negative	38 (24.5)	22 (57.9)	218 (79.0)	136 (41.3)	127 (25.1)	69 (42.9)	13 (50.0)	10 (55.6)	15 (38.5)
Positive	117 (75.5)	16 (42.1)	58 (21.0)	193 (58.7)	378 (74.9)	92 (57.1)	13 (50.0)	8 (44.4)	24 (61.5)
Missing, n	95	16	88	158	194	63	14	13	8
***ERBB2* status**, n (%)									
Negative	96 (83.5)	20 (87.0)	200 (93.5)	220 (85.3)	300 (79.4)	94 (79.7)	17 (89.5)	16 (100.0)	17 (60.7)
Positive	19 (16.5)	3 (13.0)	14 (6.5)	38 (14.7)	78 (20.6)	24 (20.3)	2 (10.5)	0 (0.0)	11 (39.3)
Missing, n	135	31	150	229	321	106	21	15	19
Surgery, n (%)									
No surgery	4 (2.2)	0 (0.0)	9 (3.6)	13 (3.8)	10 (1.9)	6 (3.5)	0 (0.0)	1 (3.8)	0 (0.0)
Breast saving	54 (30.3)	21 (53.8)	76 (30.4)	88 (25.9)	178 (33.9)	47 (27.5)	9 (31.0)	6 (23.1)	9 (32.1)
Mastectomy (with/without axillary)	49 (27.5)	9 (23.1)	97 (38.8)	101 (29.7)	190 (36.2)	63 (36.8)	10 (34.5)	3 (11.5)	11 (39.3)

Type unknown	71 (39.9)	9 (23.1)	68 (27.2)	138 (40.6)	147 (28.0)	55 (32.2)	10 (34.5)	16 (61.5)	8 (28.6)
Missing, n	72	15	114	147	174	53	11	5	19
Radiation, n (%)									
No radiation	39 (21.8)	7 (18.9)	67 (26.5)	81 (23.4)	151 (27.6)	53 (31.0)	8 (25.0)	8 (30.8)	10 (37.0)
Breast	45 (25.1)	17 (45.9)	65 (25.7)	72 (20.8)	173 (31.6)	48 (28.1)	9 (28.1)	3 (11.5)	9 (33.3)
Breast and lymph nodes	19 (10.6)	1 (2.7)	14 (5.5)	30 (8.7)	59 (10.8)	19 (11.1)	3 (9.4)	1 (3.8)	1 (3.7)
Lymph nodes only	5 (2.8)	1 (2.7)	3 (1.2)	13 (3.8)	7 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	2 (7.4)
Organ unknown	71 (39.7)	11 (29.7)	104 (41.1)	150 (43.4)	157 (28.7)	51 (29.8)	12 (37.5)	14 (53.8)	5 (18.5)
Missing, n	71	17	111	141	152	53	8	5	20
Neoadjuvant chemotherapy, n (%)									
No	152 (89.9)	35 (100.0)	201 (83.8)	270 (87.1)	397 (90.0)	132 (94.3)	24 (82.8)	21 (95.5)	25 (92.6)
Yes	17 (10.1)	0 (0.0)	39 (16.2)	40 (12.9)	44 (10.0)	8 (5.7)	5 (17.2)	1 (4.5)	2 (7.4)
Missing, n	81	19	124	177	258	84	11	9	20
Adjuvant chemotherapy, n (%)									
No	101 (56.7)	19 (54.3)	75 (30.1)	152 (45.8)	311 (59)	80 (49.1)	17 (58.6)	15 (60.0)	11 (42.3)
Yes	77 (43.3)	16 (45.7)	174 (69.9)	180 (54.2)	216 (41.0)	83 (50.9)	12 (41.4)	10 (40.0)	15 (57.7)
Missing, n	72	19	115	155	172	61	11	6	21
Endocrine therapy, n (%)									
No	51 (29.0)	18 (48.6)	164 (66.7)	106 (32.1)	178 (33.5)	59 (35.5)	12 (40.0)	15 (57.7)	7 (26.9)
Yes	125 (71.0)	19 (51.4)	82 (33.3)	224 (67.9)	353 (66.5)	107 (64.5)	18 (60.0)	11 (42.3)	19 (73.1)
Missing, n	74	17	118	157	168	58	10	5	21
Trastuzumab, n (%)									
No	108 (97.3)	31 (100.0)	168 (98.8)	193 (98.0)	319 (94.4)	87 (92.6)	17 (100.0)	9 (100.0)	19 (82.6)
Yes	3 (2.7)	0 (0.0)	2 (1.2)	4 (2.0)	19 (5.6)	7 (7.4)	0 (0.0)	0 (0.0)	4 (17.4)
Missing, n	139	23	194	290	361	130	23	22	24

Abbreviations: BC= breast cancer; IQR = interquartile range; CBC = contralateral breast cancer; ER = estrogen receptor; PR = progesterone receptor; *ERBB2* = ERB-B2 receptor tyrosine kinase 2; PTVs = protein-truncating variants; P/LP = pathogenic/likely pathogenic; MSVs = missense variants.

Percentages are given within women with no missing values.

Table S4. Characteristics of the study sample and breast tumors, overall and by ER status of the first breast cancer, including women who developed a contralateral breast cancer before study entry or within 3 months after date of first breast cancer diagnosis.

	All	ER-positive first BC	ER-negative first BC
Number of women	35232	23098	5759
Number of all-cause deaths	7114	4326	1490
Number of breast cancer-specific deaths	3556	2053	852
Number of contralateral breast cancers	1523	941	233
Age at CBC diagnosis, median (IQR)	59 (50-68)	59 (51-68)	55 (46-66)
Missing, n	74	63	6
Characteristics of the first BC			
Age at diagnosis, median (IQR)	56 (48-64)	57 (49-65)	54 (45-62)
Year of diagnosis, median (IQR)	2003 (1999-	2003 (2000-2006)	2002 (1999-2005)
Missing, n	468	322	93
Nodal status, n (%)			
Negative	18704 (63.6)	13324 (63.6)	3111 (60.3)
Positive	10696 (36.4)	7611 (36.4)	2044 (39.7)
Missing, n	5832	2163	604
Tumor size, n (%)			
≤2cm	17645 (65.4)	12900 (67.4)	2438 (53.0)
>2cm and ≤5cm	8443 (31.3)	5675 (29.7)	1923 (41.8)
>5cm	896 (3.3)	553 (2.9)	238 (5.2)
Missing, n	8248	3970	1160
Tumor grade, n (%)			
1	5825 (20.3)	4880 (23.8)	238 (4.7)
2	14239 (49.5)	11266 (55.0)	1438 (28.5)
3	8693 (30.2)	4335 (21.2)	3363 (66.7)
Missing, n	6475	2617	720
ER status, n (%)			
Negative	5759 (20.0)	-	5759 (100.0)
Positive	23098 (80.0)	23098 (100.0)	-
Missing, n	6375	-	-
PR status, n (%)			
Negative	8032 (32.5)	3564 (18.3)	4441 (85.9)
Positive	16659 (67.5)	15899 (81.7)	729 (14.1)
Missing, n	10541	3635	589
***ERBB2* status**, n (%)			
Negative	15541 (82.7)	12774 (86.0)	2632 (69.8)
Positive	3251 (17.3)	2087 (14.0)	1141 (30.2)
Missing, n	16440	8237	1986
Surgery, n (%)			
No surgery	560 (2.2)	194 (1.2)	49 (1.1)
Breast saving	8594 (34.3)	6490 (38.8)	1548 (35.8)
Mastectomy (with or without axillary)	6722 (26.8)	4374 (26.1)	1512 (35.0)
Type unknown	9181 (36.6)	5678 (33.9)	1212 (28.0)
Missing, n	10175	6362	1438
Radiation, n (%)			
No radiation	6756 (26.5)	4067 (23.8)	1110 (25.8)
Breast	7205 (28.3)	5457 (31.9)	1251 (29.1)
Breast and lymph nodes	2081 (8.2)	1495 (8.7)	487 (11.3)
Lymph nodes only	324 (1.3)	260 (1.5)	52 (1.2)
Organ unknown	9115 (35.8)	5830 (34.1)	1399 (32.5)
Missing, n	9751	5989	1460
Neoadjuvant chemotherapy, n (%)			
No	20517 (93.9)	13772 (94.9)	3396 (89.1)
Yes	1332 (6.1)	733 (5.1)	414 (10.9)
Missing, n	13383	8593	1949
Adjuvant chemotherapy, n (%)			
No	15178 (61.9)	10730 (65.0)	1522 (36.2)
Yes	9327 (38.1)	5770 (35.0)	2680 (63.8)
Missing, n	10727	6598	1557
Endocrine therapy, n (%)			
No	7714 (31.0)	3071 (18.3)	3029 (73.6)
Yes	17156 (69.0)	13742 (81.7)	1088 (26.4)
Missing, n	10362	6285	1642
Trastuzumab, n (%)			

No	14342 (96.1)	9010 (96.3)	2606 (92.1)
Yes	578 (3.9)	346 (3.7)	224 (7.9)
Missing, n	20312	13742	2929

Abbreviations: BC = breast cancer; IQR = interquartile range; CBC = contralateral breast cancer; ER = estrogen receptor; PR = progesterone receptor; *ERBB2* = ERB-B2 receptor tyrosine kinase 2.
Percentages are given within women with no missing values.

Table S5. Overview of the variables included for multiple imputation with the R package MICE.

Variable	Missing data percentage[a]	Pre-processing performed before imputation	Imputation method
Time to CBC	0.1	If CBC status missing, then set to time to last follow-up	Predictive mean matching
Year of diagnosis	1.3		Predictive mean matching
Morphology group of the tumor	6.3		Polytomous regression
CBC status[b]	10.5		Predictive mean matching
Lymph node status	16.6		Logistic regression
ER status	18.1		Logistic regression
Histopathological grade	18.4		Polytomous regression
Number of positive lymph nodes	22.0		Predictive mean matching
Size category of the tumor	23.4		Polytomous regression
Tumor stage	26.2		Polytomous regression
Radiation	27.7		Polytomous regression
Surgery	28.9		Polytomous regression
Adjuvant ET	29.4		Logistic regression
PR status	29.9		Logistic regression
Tumor size in mm	30.0		Predictive mean matching
Adjuvant CT	30.4		Logistic regression
Neoadjuvant CT	38.0		Logistic regression
Anthracyclines (neoadjuvant)	40.0		Logistic regression
Taxanes (neoadjuvant)	40.0		Logistic regression
CMF-like CT (neoadjuvant)	40.0		Logistic regression
Anthracyclines (adjuvant)	40.9		Logistic regression
CMF-like CT (adjuvant)	40.9		Logistic regression
Taxanes (adjuvant)	41.2		Logistic regression
Aromatase inhibitor	41.5		Logistic regression
Tamoxifen	41.5		Logistic regression
ERBB2 status	46.7		Logistic regression
Trastuzumab	57.7	If missing and corresponding value of Year of diagnosis observed and < 1998, then set equal to 0 (=no trastuzumab).	Logistic regression
Distant metastases status	58.6		Logistic regression

Abbreviations: CBC = contralateral breast cancer; ER = estrogen receptor; PR = progesterone receptor; *ERBB2* = ERB-B2 receptor tyrosine kinase 2; CT = chemotherapy; ET = endocrine therapy; CMF = Cyclophosphamide Methotrexate Fluorouracil.

[a] Based on the total number of women included in the imputation process (N=35232) as specified in Table S4.

[b] Event indicator for CBC.

The Nelson-Aalen estimator of the baseline cumulative hazard and the event indicator of breast cancer-specific survival and overall survival were included in all imputation models to improve imputation, as well as the time to contralateral breast cancer and the corresponding event indicator.

Table S6. Number of contralateral breast cancers from all studies and corresponding percentages of protein-truncating variants carriers in 9 breast cancer genes and pathogenic/likely pathogenic rare missense variants carriers in *BRCA1*, *BRCA2* and *TP53*, overall and by subgroups based on age.

Selection	Total number of CBCs, n	Carriers in 9 BC genes, n (PTVs + P/LP MSVs,%)	*ATM* PTVs carriers, n (%)	*BARD1* PTVs carriers, n (%)	*BRCA1* carriers, n (PTVs + P/LP MSVs, %)	*BRCA2* carriers, n (PTVs + P/LP MSVs, %)	*CHEK2* PTVs carriers, n (%)	*PALB2* PTVs carriers, n (%)	*RAD51C* PTVs carriers, n (%)	*RAD51D* PTVs carriers, n (%)	*TP53* carriers, n (PTVs + P/LP MSVs, %)
Numbers and percentages of CBCs from the sample of 35232 women used for multiple imputation (as in Table S4), including women with unknown time to CBC and women who developed a CBC before study entry or within 3 months after date of first breast cancer diagnosis											
All CBCs [a]	1523	189 (12.4)	12 (0.8)	5 (0.3)	32 (2.1)	44 (2.9)	69 (4.5)	18 (1.2)	4 (0.3)	2 (0.1)	11 (0.7)
CBCs diagnosed at age < 50 years	344	74 (21.5)	4 (1.2)	0 (0.0)	19 (5.5)	19 (5.5)	23 (6.7)	3 (0.9)	1 (0.3)	0 (0.0)	9 (2.6)
CBCs diagnosed at age ≥ 50 years	1105	111 (10.0)	8 (0.7)	5 (0.5)	13 (1.2)	23 (2.1)	44 (4.0)	15 (1.4)	3 (0.3)	2 (0.2)	2 (0.2)
Missing age at diagnosis of CBC	74	4 (5.4)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.7)	2 (2.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Numbers and percentages of CBCs from the sample of 30628 women included in the CBC risk analyses, excluding women with unknown time to CBC and women who developed a CBC before study entry or within 3 months after date of first breast cancer diagnosis											
All CBCs [b]	676	103 (15.2)	6 (0.9)	2 (0.3)	21 (3.1)	20 (3.0)	38 (5.6)	11 (1.6)	2 (0.3)	1 (0.1)	5 (0.7)
CBCs diagnosed at age < 50 years	127	40 (31.5)	0 (0.0)	0 (0.0)	11 (8.7)	9 (7.1)	14 (11.0)	3 (2.4)	0 (0.0)	0 (0.0)	5 (3.9)
CBCs diagnosed at age ≥ 50 years	549	63 (11.5)	6 (1.1)	2 (0.4)	10 (1.8)	11 (2.0)	24 (4.4)	8 (1.5)	2 (0.4)	1 (0.2)	0 (0.0)

Abbreviations**:** BC = breast cancer; CBC = contralateral breast cancer; PTVs = protein-truncating variants; P/LP = pathogenic/likely pathogenic; MSVs = missense variants.

In each row, percentages corresponding to separate genes do not exactly sum up to the percentage of carriers in any of the 9 BC genes due to the fact that some women carry mutations in more than one gene.

[a] All considered including invasive (68.7), in-situ (11.0), and missing behavior (20.4).
[b] All considered including invasive (70.7), in-situ (10.9), and missing behavior (18.3).

Table S7. **Association of protein-truncating variants in 9 breast cancer genes and of pathogenic/likely pathogenic rare missense variants in *BRCA1*, *BRCA2* and *TP53* with risk of contralateral breast cancer in women diagnosed with ER-positive first breast cancer.**

Gene	Unadjusted analyses		Adjusted analyses[a]		No. of women		No. of CBC	
PTVs (unless indicated otherwise)	**HR (95%CI)**	**P**	**HR (95%CI)**	**P**	**Non-carriers**	**Carriers**	**Non-carriers**	**Carriers**
ATM	1.22 (0.44-3.39)	7.0E-01	1.25 (0.45-3.52)	6.7E-01	19733	144	414	4
BARD1	NA	NA	NA	NA	19854	23	418	0
BRCA1[b]	1.53 (0.34-6.76)	5.8E-01	1.62 (0.36-7.31)	5.3E-01	19800	77	416	2
BRCA2[b]	**2.66 (1.40-5.04)**	**2.7E-03**	**2.66 (1.40-5.09)**	**3.1E-03**	19634	243	405	13
CHEK2	**2.11 (1.35-3.29)**	**1.0E-03**	**2.06 (1.31-3.22)**	**1.7E-03**	19412	465	392	26
c.1100delC	**2.48 (1.56-3.94)**	**1.3E-04**	**2.45 (1.53-3.91)**	**1.9E-04**	19412	384	392	25
Other	0.45 (0.08-2.48)	3.6E-01	0.41 (0.08-2.24)	3.0E-01	19412	81	392	1
PALB2	2.49 (0.97-6.35)	5.7E-02	2.57 (0.99-6.64)	5.2E-02	19761	116	412	6
RAD51C	NA	NA	NA	NA	19859	18	418	0
RAD51D	NA	NA	NA	NA	19866	11	418	0
TP53[b]	**10.33 (2.66-40.12)**	**7.4E-04**	**10.74 (2.72-42.38)**	**7.4E-04**	19851	26	414	4

Abbreviations: No. = number; CBC = contralateral breast cancer; PTVs = protein-truncating variants; HR = hazard ratio; CI = confidence interval; P = p-value.

Analyses included women from 32 studies with information about contralateral breast cancer diagnosis. Statistically significant associations (P<5E-02) are highlighted in bold. NA: not assessable due to absence of mutation carriers with events.

[a] Adjusted analyses were performed by including age at diagnosis, nodal status, size category, grade, ERB-B2 receptor tyrosine kinase 2 (*ERBB2*) status of the first breast cancer, (neo)adjuvant chemotherapy, endocrine therapy and trastuzumab as covariates in the Cox regression model.

[b] Combined PTVs and rare pathogenic/likely pathogenic missense variants as defined in Dorling et al. (NEJM 2021).

Table S8. **Association of protein-truncating variants in 9 breast cancer genes and of pathogenic/likely pathogenic rare missense variants in *BRCA1*, *BRCA2* and *TP53* with risk of contralateral breast cancer in women diagnosed with ER-negative first breast cancer.**

Gene	Unadjusted analyses		Adjusted analyses[a]		No. of women		No of CBC	
PTVs (unless indicated otherwise)	**HR (95%CI)**	**P**	**HR (95%CI)**	**P**	**Non-carriers**	**Carriers**	**Non-carriers**	**Carriers**
ATM	NA	NA	NA	NA	5016	22	139	0
BARD1	2.01 (0.22-18.18)	5.3E-01	1.76 (0.20-15.72)	6.1E-01	5020	18	138	1
BRCA1[b]	**2.96 (1.62-5.43)**	**4.4E-04**	**2.98 (1.58-5.63)**	**9.3E-04**	4844	194	123	16
BRCA2[b]	1.26 (0.38-4.13)	7.1E-01	1.19 (0.36-3.94)	7.E-01	4951	87	136	3
CHEK2	2.48 (0.96-6.36)	5.9E-02	2.50 (0.95-6.57)	6.3E-02	4965	73	133	6
c.1100delC	1.37 (0.41-4.63)	6.1E-01	1.36 (0.39-4.69)	6.2E-01	4965	54	133	3
Other	**10.44(2.16-50.50)**	**3.5E-03**	**11.9 (2.32-61.19)**	**3.3E-03**	4965	19	133	3
PALB2	2.55 (0.68 - 9.56)	1.6E-01	2.69 (0.70-10.37)	1.5E-01	4995	43	136	3
RAD51C	2.35 (0.25-22.25)	4.6E-01	2.31 (0.24-22.62)	4.7E-01	5027	11	138	1
RAD51D	2.44 (0.25-24.01)	4.5E-01	1.87 (0.20-17.56)	5.8E-01	5027	11	138	1
TP53[b]	4.87 (0.41-58.18)	2.1E-01	4.75 (0.38-58.74)	2.2E-01	5029	9	138	1

Abbreviations: No. = number; CBC = contralateral breast cancer; PTVs = protein-truncating variants; HR = hazard ratio; CI = confidence interval; P = p-value.

Analyses included women from 32 studies with information about contralateral breast cancer diagnosis. Statistically significant associations (P<5E-02) are highlighted in bold. NA: not assessable due to absence of mutation carriers with events.

[a] Adjusted analyses were performed by including age at diagnosis, nodal status, size category, grade, ERB-B2 receptor tyrosine kinase 2 (*ERBB2*) status of the first breast cancer, (neo)adjuvant chemotherapy, endocrine therapy and trastuzumab as covariates in the Cox regression model.

[b] Combined PTVs and rare pathogenic/likely pathogenic missense variants as defined in Dorling et al. (NEJM 2021).

Table S9. Heterogeneity test for the association of protein-truncating variants in 9 breast cancer genes and of pathogenic/likely pathogenic rare missense variants in *BRCA1*, *BRCA2* and *TP53* with contralateral breast cancer risk and breast cancer-specific survival, by ER status of the first breast cancer.

Gene	Contralateral breast cancer risk		Breast cancer-specific survival	
PTVs (unless indicated otherwise)	**P**	**P[a]**	**P**	**P[a]**
ATM	1.5E-01	9.9E-01	4.6E-01	5.4E-01
BARD1	2.5E-01	9.9E-01	6.3E-01	2.8E-01
BRCA1[b]	2.7E-01	3.7E-01	**8.8E-03**	**1.5E-02**
BRCA2[b]	3.1E-01	3.1E-01	**6.4E-04**	**2.2E-02**
CHEK2	7.8E-01	7.7E-01	4.8E-01	4.6E-01
PALB2	9.5E-01	9.7E-01	3.3E-01	7.4E-01
RAD51C	NA	NA	NA	NA
RAD51D	NA	NA	9.8E-01	8.6E-01
TP53[b]	4.6E-01	4.6E-01	2.0E-01	5.7E-01

Abbreviations: P = p-value; PTVs = protein-truncating variants.

Heterogeneity tests are for the hazard ratio (HR) estimates presented in Tables S7-S8 (contralateral breast cancer risk) and S26-S27 (breast cancer-specific survival) and compare a model including main effects and an interaction term between the mutation carrier status and the ER status of the first breast cancer, with a model without the interaction term. Statistically significant associations (P<5E-02) are highlighted in bold. NA: not assessable within ER-positive and/or ER-negative tumors due to absence of mutation carriers or of mutation carriers with events.

[a] The two models compared additionally include the covariates specified in Tables S7-S8 and S26-S27.

[b] Combined PTVs and rare pathogenic/likely pathogenic missense variants as defined in Dorling et al. (NEJM 2021).

Table S10. **Association of rare missense variants in 9 breast cancer genes with risk of contralateral breast cancer.**

Gene	Unadjusted analyses		Adjusted analyses[a]		No. of women		No. of CBC	
	HR (95%CI)	P	HR (95%CI)	P	Non-carriers	Carriers	Non-carriers	Carriers
ATM	1.33 (0.97-1.81)	7.4E-02	1.34 (0.98-1.84)	6.2E-02	28846	1553	622	48
BARD1	0.79 (0.37-1.72)	5.6E-01	0.80 (0.37-1.73)	5.7E-01	30226	351	668	6
BRCA1	1.44 (0.94-2.19)	9.4E-02	1.44 (0.94-2.21)	9.2E-02	29521	817	631	25
BRCA2	1.33 (0.98-1.82)	6.9E-02	1.34 (0.98-1.83)	6.7E-02	28627	1612	612	47
CHEK2	**1.78 (1.08-2.93)**	**2.4E-02**	**1.78 (1.08-2.94)**	**2.5E-02**	29420	552	619	19
PALB2	0.63 (0.28-1.41)	2.6E-01	0.63 (0.28-1.43)	2.7E-01	30025	403	660	5
RAD51C	0.79 (0.21-3.00)	7.3E-01	0.78 (0.21-2.98)	7.2E-01	30468	123	672	2
RAD51D	1.36 (0.41-4.49)	6.1E-01	1.43 (0.43-4.77)	5.6E-01	30498	101	672	3
TP53	**2.40 (1.08-5.32)**	**3.2E-02**	**2.54 (1.13-5.69)**	**2.4E-02**	30461	165	668	8

Abbreviations: No. = number; CBC = contralateral breast cancer; HR = hazard ratio; CI = confidence interval; P = p-value. Analyses included women from 32 studies with information about contralateral breast cancer diagnosis. The analysis for each gene excluded carriers of protein-truncating variants in that gene. Statistically significant associations (P<5E-02) are highlighted in bold.

[a] Adjusted analyses were performed by including age at diagnosis, nodal status, size category, grade, estrogen receptor (ER) status, ERB-B2 receptor tyrosine kinase 2 (*ERBB2*) status of the first breast cancer, (neo)adjuvant chemotherapy, endocrine therapy and trastuzumab as covariates in the Cox regression model.

Table S11. **Association of rare missense variants in 9 breast cancer genes with risk of contralateral breast cancer in women diagnosed with ER-positive first breast cancer.**

Gene	Unadjusted analyses		Adjusted analyses[a]		No. of women		No. of CBC	
	HR (95%CI)	P	HR (95%CI)	P	Non-carriers	Carriers	Non-carriers	Carriers
ATM	1.38 (0.93-2.05)	1.1E-01	1.40 (0.94-2.08)	1.0E-01	18721	1012	385	29
BARD1	0.64 (0.22-1.84)	4.1E-01	0.64 (0.22-1.84)	4.1E-01	19628	226	415	3
BRCA1	1.56 (0.93-2.63)	9.3E-02	1.58 (0.94-2.67)	8.6E-02	19289	521	400	17
BRCA2	1.31 (0.88-1.94)	1.8E-01	1.32 (0.88-1.96)	1.7E-01	18637	1014	377	29
CHEK2	1.70 (0.88-3.26)	1.1E-01	1.67 (0.87-3.20)	1.2E-01	19029	383	381	11
PALB2	0.70 (0.28-1.78)	4.6E-01	0.71 (0.28-1.80)	4.6E-01	19481	280	408	4
RAD51C	NA	NA	NA	NA	19788	71	418	0
RAD51D	1.43 (0.33-6.24)	6.4E-01	1.54 (0.35-6.88)	5.7E-01	19802	64	416	2
TP53	2.43 (0.88-6.66)	8.6E-02	2.67 (0.95-7.50)	6.1E-02	19771	106	413	5

Abbreviations: No. = number; CBC = contralateral breast cancer; HR = hazard ratio; CI = confidence interval; P = p-value. Analyses included women from 32 studies with information about contralateral breast cancer diagnosis. The analysis for each gene excluded carriers of protein-truncating variants in that gene. NA: not assessable due to absence of mutation carriers with events.

[a] Adjusted analyses were performed by including age at diagnosis, nodal status, size category, grade, ERB-B2 receptor tyrosine kinase 2 (*ERBB2*) status of the first breast cancer, (neo)adjuvant chemotherapy, endocrine therapy and trastuzumab as covariates in the Cox regression model.

Table S12. Association of rare missense variants in 9 breast cancer genes with risk of contralateral breast cancer in women diagnosed with ER-negative first breast cancer.

Gene	Unadjusted analyses		Adjusted analyses[a]		No. of women		No. of CBC	
	HR (95%CI)	P	HR (95%CI)	P	Non-carriers	Carriers	Non-carriers	Carriers
ATM	1.35 (0.71-2.59)	3.6E-01	1.38 (0.71-2.68)	3.3E-01	4756	260	127	12
BARD1	0.57 (0.10-3.44)	5.4E-01	0.55 (0.09-3.33)	5.1E-01	4954	66	137	1
BRCA1	1.50 (0.62-3.62)	3.6E-01	1.51 (0.62-3.72)	3.6E-01	4712	156	117	6
BRCA2	1.30 (0.66-2.54)	4.4E-01	1.28 (0.65-2.52)	4.8E-01	4663	293	127	10
CHEK2	1.12 (0.27-4.76)	8.7E-01	1.13 (0.25-5.01)	8.7E-01	4907	58	131	2
PALB2	0.82 (0.12-5.51)	8.4E-01	0.86 (0.12-6.06)	8.8E-01	4937	58	135	1
RAD51C	1.16 (0.15-9.24)	8.9E-01	1.08 (0.13-8.66)	9.4E-01	4999	28	137	1
RAD51D	1.90 (0.21-16.86)	5.7E-01	1.65 (0.19-14.62)	6.5E-01	5007	20	137	1
TP53	1.96 (0.41-9.27)	4.0E-01	2.01 (0.41-9.79)	3.9E-01	5003	33	137	2

Abbreviations: No. = number; CBC = contralateral breast cancer; HR = hazard ratio; CI = confidence interval; P = p-value. Analyses included women from 32 studies with information about contralateral breast cancer diagnosis. The analysis for each gene excluded carriers of protein-truncating variants in that gene.

[a] Adjusted analyses were performed by including age at diagnosis, nodal status, size category, grade, ERB-B2 receptor tyrosine kinase 2 (*ERBB2*) status of the first breast cancer, (neo)adjuvant chemotherapy, endocrine therapy and trastuzumab as covariates in the Cox regression model.

Table S13. Heterogeneity test for the association of rare missense variants in 9 breast cancer genes with contralateral breast cancer risk and breast cancer-specific survival, by ER status of the first breast cancer.

Gene	Contralateral breast cancer risk		Breast cancer-specific survival	
	P	P[a]	P	P[a]
ATM	9.9E-01	9.8E-01	3.8E-01	4.5E-01
BARD1	8.4E-01	8.7E-01	3.9E-01	5.4E-01
BRCA1	9.1E-01	9.3E-01	5.8E-01	6.2E-01
BRCA2	9.2E-01	8.8E-01	4.8E-01	7.3E-01
CHEK2	6.2E-01	6.5E-01	3.4E-01	3.3E-01
PALB2	8.7E-01	8.6E-01	5.2E-01	4.9E-01
RAD51C	NA	NA	8.9E-01	8.0E-01
RAD51D	8.8E-01	8.6E-01	6.1E-01	7.7E-01
TP53	8.5E-01	7.5E-01	1.2E-01	4.6E-01

Abbreviation: P = p-value.

Heterogeneity tests are for the hazard ratio (HR) estimates presented in Tables S11-S12 (contralateral breast cancer risk) and S29-S30 (breast cancer-specific survival) and compare a model including main effects and an interaction term between the mutation carrier status and the ER status of the first breast cancer, with a model without the interaction term.

NA: not assessable within ER-positive and/or ER-negative tumors due to absence of mutation carriers or of mutation carriers with events.

[a] The two model compared additionally include the covariates specified in Tables S11-S12 and S29-S30.

Table S14. Sensitivity analyses for the association of protein-truncating variants and of pathogenic/likely pathogenic rare missense variants in *BRCA1*, *BRCA2* and *TP53* in 9 breast cancer genes with risk of contralateral breast cancer, with the set of non-carriers restricted to women who do not carry protein-truncating variants in any of the 9 breast cancer genes nor pathogenic/likely pathogenic rare missense variants in *BRCA1*, *BRCA2* and *TP53*.

Gene	Unadjusted analyses		Adjusted analyses[a]		No. of women		No. of CBC	
PTVs (unless indicated otherwise)	**HR (95%CI)**	**P**	**HR (95%CI)**	**P**	**Non-carriers**	**Carriers**	**Non-carriers**	**Carriers**
ATM	1.12 (0.46-2.75)	8.1E-01	1.17 (0.47-2.92)	7.3E-01	28668	221	573	5
BARD1	1.16 (0.16-8.68)	8.8E-01	1.13 (0.15-8.44)	9.0E-01	28668	47	573	1
BRCA1[b]	**3.04 (1.80-5.15)**	**3.4E-05**	**3.21 (1.86-5.54)**	**3.3E-05**	28668	321	573	20
BRCA2[b]	**2.56 (1.54-4.28)**	**3.2E-04**	**2.71 (1.61-4.56)**	**1.9E-04**	28668	409	573	20
CHEK2	**2.36 (1.61-3.47)**	**1.1E-05**	**2.35 (1.59-3.45)**	**1.7E-05**	28668	632	573	36
c.1100delC	**2.51 (1.67-3.79)**	**1.0E-05**	**2.50 (1.65-3.77)**	**1.6E-05**	28668	512	573	32
Other	1.60 (0.56-4.64)	3.8E-01	1.57 (0.54-4.53)	4.1E-01	28668	120	573	4
PALB2	**2.94 (1.46-5.93)**	**2.6E-03**	**3.10 (1.52-6.30)**	**1.9E-03**	28668	199	573	11
RAD51C	2.84 (0.56-14.48)	2.1E-01	2.80 (0.55-14.33)	2.2E-01	28668	33	573	2
RAD51D	1.91 (0.22-16.83)	5.6E-01	1.84 (0.21-16.19)	5.8E-01	28668	27	573	1
TP53[b]	**7.63 (2.06-28.25)**	**2.3E-03**	**8.52 (2.25-32.28)**	**1.7E-03**	28668	38	573	4

Abbreviations: No. = number; CBC = contralateral breast cancer; PTVs = protein-truncating variants HR = hazard ratio; CI = confidence interval; P = p-value.

Analyses included women from 32 studies with information about contralateral breast cancer diagnosis. Statistically significant associations (P<5E-02) are highlighted in bold. NA: not assessable due to absence of mutation carriers with events.

[a] Adjusted analyses were performed by including age at diagnosis, nodal status, size category, grade, estrogen receptor (ER) status, ERB-B2 receptor tyrosine kinase 2 (*ERBB2*) status of the first breast cancer, (neo)adjuvant chemotherapy, endocrine therapy and trastuzumab as covariates in the Cox regression model.

[b] Combined PTVs and rare pathogenic/likely pathogenic missense variants as defined in Dorling et al. (NEJM 2021).

Table S15. **Sensitivity analysis for the association of rare missense variants in 9 breast cancer genes with risk of contralateral breast cancer, with the set of non-carriers restricted to women who do not carry protein-truncating variants in any of the 9 breast cancer genes nor pathogenic/likely pathogenic rare missense variants in *BRCA1*, *BRCA2* and *TP53*.**

Gene	Unadjusted analyses		Adjusted analyses[a]		No. of women		No. of CBC	
	HR (95%CI)	P	HR (95%CI)	P	Non-carriers	Carriers	Non-carriers	Carriers
ATM	1.37 (0.99-1.91)	6.1E-02	1.39 (1.00-1.94)	5.2E-02	27198	1470	530	43
BARD1	0.75 (0.32-1.74)	5.1E-01	0.76 (0.33-1.76)	5.2E-01	28338	330	568	5
BRCA1	1.43 (0.90-2.28)	1.3E-01	1.44 (0.91-2.30)	1.2E-01	27928	740	552	21
BRCA2	1.24 (0.89-1.75)	2.1E-01	1.26 (0.89-1.77)	1.9E-01	27157	1511	535	38
CHEK2	**1.71 (1.01-2.90)**	**4.4E-02**	**1.73 (1.02-2.93)**	**4.3E-02**	28132	536	556	17
PALB2	**0.29 (0.10-0.87)**	**2.8E-02**	**0.29 (0.10-0.88)**	**2.9E-02**	28291	377	571	2
RAD51C	0.93 (0.23-3.66)	9.1E-01	0.92 (0.23-3.65)	9.1E-01	28555	113	571	2
RAD51D	1.12 (0.27-4.63)	8.7E-01	1.17 (0.28-4.88)	8.3E-01	28574	94	571	2
TP53	0.88 (0.23-3.45)	8.6E-01	0.95 (0.24-3.79)	9.4E-01	28556	112	571	2

Abbreviations: No. = number; CBC = contralateral breast cancer; HR= hazard ration; CI = confidence interval; P = p-value. Analyses included women from 32 studies with information about contralateral breast cancer diagnosis. The analysis for each gene also excluded carriers of protein-truncating variants in that gene. Statistically significant associations (P<5E-02) are highlighted in bold.

[a] Adjusted analyses were performed by including age at diagnosis, nodal status, size category, grade, estrogen receptor (ER) status, ERB-B2 receptor tyrosine kinase 2 (*ERBB2*) status of the first breast cancer, (neo)adjuvant chemotherapy, endocrine therapy and trastuzumab as covariates in the Cox regression model.

Table S16. **Sensitivity analysis for the association of protein-truncating variants in 9 breast cancer genes and of pathogenic/likely pathogenic rare missense variants in *BRCA1*, *BRCA2* and *TP53* with risk of contralateral breast cancer in women from population- and hospital-based studies plus women without family history from studies including women with family history of breast cancer.**

Gene	Unadjusted analyses		Adjusted analyses[a]		No. of women		No. of CBC	
PTVs (unless indicated otherwise)	**HR (95%CI)**	**P**	**HR (95%CI)**	**P**	**Non-carriers**	**Carriers**	**Non-carriers**	**Carriers**
ATM	1.13 (0.35-3.61)	8.3E-01	1.15 (0.36-3.70)	8.1E-01	26297	179	432	3
BARD1	1.49 (0.18-12.04)	7.1E-01	1.35 (0.17-10.71)	7.8E-01	26435	41	434	1
BRCA1[b]	**3.45 (2.01-5.92)**	**6.6E-06**	**3.13 (1.80-5.45)**	**6.1E-05**	26167	309	415	20
BRCA2[b]	**2.40 (1.36-4.24)**	**2.6E-03**	**2.26 (1.27-4.00)**	**5.4E-03**	26088	388	419	16
CHEK2	**2.61 (1.58-4.32)**	**2.0E-04**	**2.65 (1.59-4.40)**	**1.9E-04**	25973	503	414	21
c.1100delC	**2.70 (1.54-4.74)**	**5.5E-04**	**2.72 (1.54-4.79)**	**5.7E-04**	25973	398	414	17
Other	2.33 (0.76-7.15)	1.4E-01	2.39 (0.77-7.41)	1.3E-01	25973	105	414	4
PALB2	**4.20 (1.94-9.07)**	**2.7E-04**	**4.00 (1.85-8.64)**	**4.5E-04**	26322	154	425	10
RAD51C	NA	NA	NA	NA	26450	26	435	0
RAD51D	2.16 (0.24-19.92)	5.0E-01	1.66 (0.19-14.18)	6.4E-01	26451	25	434	1
TP53[b]	NA	NA	NA	NA	26453	23	435	0

Abbreviations: No. = number; CBC = contralateral breast cancer; PTVs = protein-truncating variants; HR = hazard ratio; CI = confidence interval; P = p-value.

Statistically significant associations (P<5E-02) are highlighted in bold. NA: not assessable due to absence of mutation carriers with events.

[a] Adjusted analyses were performed by including age at diagnosis, nodal status, size category, grade, estrogen receptor (ER) status, ERB-B2 receptor tyrosine kinase 2 (*ERBB2*) status of the first breast cancer, (neo)adjuvant chemotherapy, endocrine therapy and trastuzumab as covariates in the Cox regression model.

[b] Combined PTVs and rare pathogenic/likely pathogenic missense variants as defined in Dorling et al. (NEJM 2021).

Table S17. **Sensitivity analysis for the association of rare missense variants in 9 breast cancer genes with risk of contralateral breast cancer in women from population- and hospital-based studies plus women without family history from studies including women with family history of breast cancer.**

Gene	Unadjusted analyses		Adjusted analyses[a]		No. of women		No. of CBC	
	HR (95%CI)	P	HR (95%CI)	P	Non-carriers	Carriers	Non-carriers	Carriers
ATM	1.18 (0.78-1.77)	4.4E-01	1.17 (0.77-1.75)	4.6E-01	25012	1285	406	26
BARD1	0.42 (0.13-1.40)	1.6E-01	0.43 (0.13-1.41)	1.6E-01	26136	299	432	2
BRCA1	1.32 (0.77-2.27)	3.1E-01	1.34 (0.78-2.30)	2.9E-01	25499	706	401	15
BRCA2	1.38 (0.94-2.03)	9.9E-02	1.37 (0.93-2.02)	1.1E-01	24740	1371	390	31
CHEK2	1.71 (0.89-3.28)	1.1E-01	1.76 (0.91-3.39)	9.2E-02	25527	446	403	11
PALB2	0.73 (0.29-1.87)	5.2E-01	0.75 (0.29-1.93)	5.5E-01	25974	348	421	4
RAD51C	NA	NA	NA	NA	26350	100	435	0
RAD51D	0.64 (0.10-3.96)	6.3E-01	0.62 (0.10-3.80)	6.0E-01	26366	85	433	1
TP53	0.53 (0.09-3.08)	4.8E-01	0.54 (0.09-3.16)	4.9E-01	26348	126	434	1

Abbreviations: No. = number; CBC = contralateral breast cancer; HR = hazard ratio; CI = confidence interval; P = p-value. The analysis for each gene excluded carriers of protein-truncating variants in that gene. NA: not assessable due to absence of mutation carriers with events.

[a] Adjusted analyses were performed by including age at diagnosis, nodal status, size category, grade, estrogen receptor (ER) status, ERB-B2 receptor tyrosine kinase 2 (*ERBB2*) status of the first breast cancer, (neo)adjuvant chemotherapy, endocrine therapy and trastuzumab as covariates in the Cox regression model.

Table S18. **Association of protein-truncating variants in 25 putative breast cancer genes with risk of contralateral breast cancer.**

Gene	Unadjusted analyses		Adjusted analyses[a]		No. of women		No. of CBC	
	HR (95%CI)	P	HR (95%CI)	P	Non-carriers	Carriers	Non-carriers	Carriers
ABRAXAS1	NA	NA	NA	NA	30618	10	676	0
AKT1	NA	NA	NA	NA	30626	2	676	0
BABAM2	NA	NA	NA	NA	30622	6	676	0
BRIP1	0.94 (0.13-6.53)	9.5E-01	1.01 (0.14-7.21)	1.0E+00	30571	57	675	1
CDH1	8.74(0.61-124.37)	1.1E-01	8.22(0.58-115.74)	1.2E-01	30622	6	675	1
EPCAM	NA	NA	NA	NA	30621	7	676	0
FANCC	1.33 (0.31-5.71)	7.0E-01	1.28 (0.30-5.50)	7.4E-01	30579	49	674	2
FANCM	0.64 (0.26-1.61)	3.5E-01	0.64 (0.26-1.61)	3.4E-01	30384	244	672	4
GEN1	6.85 (0.52-90.72)	1.4E-01	5.78 (0.46-73.22)	1.8E-01	30611	17	675	1
MEN1	NA	NA	NA	NA	30625	3	676	0
MLH1	NA	NA	NA	NA	30625	3	676	0
MRE11A	NA	NA	NA	NA	30596	32	676	0
MSH2	NA	NA	NA	NA	30619	9	676	0
MSH6	NA	NA	NA	NA	30601	27	676	0
MUTYH	NA	NA	NA	NA	30601	27	676	0
NBN	NA	NA	NA	NA	30556	72	676	0
NF1	NA	NA	NA	NA	30609	19	676	0
PIK3CA	NA	NA	NA	NA	30622	6	676	0
PMS2	NA	NA	NA	NA	30606	22	676	0
PTEN	7.14 (1.13-44.88)	3.6E-02	5.35 (0.87-32.91)	7.0E-02	30616	12	674	2
RAD50	**4.81 (1.88-12.27)**	**1.0E-03**	**4.75 (1.86-12.15)**	**1.2E-03**	30537	91	669	7
RECQL	1.95 (0.22-17.22)	5.5E-01	1.8 (0.21-15.62)	5.9E-01	30589	39	675	1
RINT1	2.92 (0.57-15.00)	2.0E-01	2.86 (0.56-14.70)	2.1E-01	30605	23	674	2
STK11	NA	NA	NA	NA	30626	2	676	0
XRCC2	NA	NA	NA	NA	30620	8	676	0

Abbreviations: No. = number; CBC = contralateral breast cancer; HR = hazard ratio; CI = confidence interval; P = p-value.

Analyses included women from 32 studies with information about contralateral breast cancer diagnosis. Statistically significant associations after Bonferroni correction for 25 tests (P<2E-03) are highlighted in bold. NA: not assessable due to absence of mutation carriers with events.

Genes on the BRIDGES panel (Dorling et al., NEJM 2021) other than *ATM*, *BARD1*, *BRCA1*, *BRCA2*, *CHEK2*, *PALB2*, *RAD51C*, *RAD51D*, and *TP53* are presented here.

[a] Adjusted analyses were performed by including age at diagnosis, nodal status, size category, grade, estrogen receptor (ER) status, ERB-B2 receptor tyrosine kinase 2 (*ERBB2*) status of the first breast cancer, (neo)adjuvant chemotherapy, endocrine therapy and trastuzumab as covariates in the Cox regression model.

Table S19. **Association of rare missense variants in 25 putative breast cancer genes with risk of contralateral breast cancer.**

Gene	Unadjusted analyses		Adjusted analyses[a]		No. of women		No. of CBC	
	HR (95%CI)	P	HR (95%CI)	P	Non-carriers	Carriers	Non-carriers	Carriers
ABRAXAS1	0.95 (0.31-2.93)	9.3E-01	0.96 (0.31-2.97)	9.4E-01	30488	130	673	3
AKT1	1.98 (0.66-5.93)	2.2E-01	2.03 (0.67-6.10)	2.1E-01	30543	83	672	4
BABAM2	NA	NA	NA	NA	30524	98	676	0
BRIP1	1.09 (0.62-1.90)	7.7E-01	1.08 (0.62-1.89)	7.9E-01	30093	478	662	13
CDH1	0.90 (0.45-1.80)	7.7E-01	0.90 (0.45-1.78)	7.5E-01	30266	356	667	8
EPCAM	2.22 (1.01-4.89)	4.7E-02	2.27 (1.02-5.03)	4.4E-02	30482	139	668	8
FANCC	0.72 (0.34-1.54)	3.9E-01	0.74 (0.34-1.58)	4.3E-01	30212	367	668	6
FANCM	0.98 (0.62-1.55)	9.4E-01	0.98 (0.62-1.54)	9.2E-01	29497	887	653	19
GEN1	0.43 (0.18–1.00)	5.0E-02	0.42 (0.18-0.98)	4.6E-02	30228	383	671	4
MEN1	0.66 (0.11-4.07)	6.5E-01	0.71 (0.11-4.53)	7.2E-01	30548	77	675	1
MLH1	1.05 (0.56-1.98)	8.7E-01	1.09 (0.58-2.06)	7.9E-01	30190	435	666	10
MRE11A	1.27 (0.64-2.52)	4.9E-01	1.29 (0.65-2.58)	4.6E-01	30251	345	667	9
MSH2	0.57 (0.27-1.18)	1.3E-01	0.58 (0.28-1.21)	1.4E-01	30141	478	670	6
MSH6	1.08 (0.64-1.81)	7.7E-01	1.07 (0.64-1.80)	8.0E-01	29974	627	660	16
MUTYH	0.69 (0.30-1.58)	3.8E-01	0.68 (0.30-1.56)	3.6E-01	30255	346	671	5
NBN	1.49 (0.81-2.74)	2.0E-01	1.48 (0.80-2.73)	2.1E-01	30190	366	664	12
NF1	1.48 (0.86-2.55)	1.6E-01	1.52 (0.88-2.64)	1.3E-01	30117	492	661	15
PIK3CA	0.73 (0.19-2.71)	6.3E-01	0.72 (0.19-2.68)	6.2E-01	30504	118	674	2
PMS2	1.69 (1.02-2.81)	4.3E-02	1.68 (1.01-2.79)	4.6E-02	30049	557	658	18
PTEN	NA	NA	NA	NA	30561	55	674	0
RAD50	1.36 (0.85-2.18)	1.9E-01	1.36 (0.85-2.18)	2.0E-01	29882	655	649	20
RECQL	0.66 (0.29-1.51)	3.3E-01	0.68 (0.30-1.56)	3.6E-01	30250	339	670	5
RINT1	1.03 (0.57-1.88)	9.2E-01	1.00 (0.55-1.81)	9.9E-01	30152	453	663	11
STK11	1.04 (0.14-7.47)	9.7E-01	1.04 (0.14-7.57)	9.7E-01	30573	53	675	1
XRCC2	**3.87 (1.81-8.29)**	**5.0E-04**	**4.05 (1.88-8.73)**	**3.8E-04**	30494	126	666	10

Abbreviations: No. = number; CBC = contralateral breast cancer; HR = hazard ratio; CI = confidence interval; P = p-value.
Analyses included women from 32 studies with information about contralateral breast cancer diagnosis. Statistically significant associations after Bonferroni correction for 25 tests (P<2E-03) are highlighted in bold. NA: not assessable due to absence of mutation carriers with events.

Genes on the BRIDGES panel (Dorling et al., NEJM 2021) other than *ATM*, *BARD1*, *BRCA1*, *BRCA2*, *CHEK2*, *PALB2*, *RAD51C*, *RAD51D*, and *TP53* are presented here.

[a] Adjusted analyses were performed by including age at diagnosis, nodal status, size category, grade, estrogen receptor (ER) status, ERB-B2 receptor tyrosine kinase 2 (*ERBB2*) status of the first breast cancer, (neo)adjuvant chemotherapy, endocrine therapy and trastuzumab as covariates in the Cox regression model. The analysis for each gene excluded carriers of protein-truncating variants in that gene.

Table S20. **Association of protein-truncating variants in 25 putative breast cancer genes with risk of contralateral breast cancer in women diagnosed with ER-positive first breast cancer.**

Gene	Unadjusted analyses		Adjusted analyses[a]		No. of women		No. of CBC	
	HR (95%CI)	P	HR (95%CI)	P	Non-carriers	Carriers	Non-carriers	Carriers
ABRAXAS1	NA	NA	NA	NA	19871	6	418	0
AKT1	NA	NA	NA	NA	19875	2	418	0
BABAM2	NA	NA	NA	NA	19872	5	418	0
BRIP1	NA	NA	NA	NA	19847	30	418	0
CDH1	11.54 (0.74-179.25)	8.1E-02	9.79 (0.65-146.35)	9.8E-02	19873	4	417	1
EPCAM	NA	NA	NA	NA	19872	5	418	0
FANCC	1.31 (0.17-10.28)	8.0E-01	1.32 (0.17-10.52)	7.9E-01	19849	28	417	1
FANCM	0.97 (0.36-2.59)	9.5E-01	0.97 (0.36-2.63)	9.6E-01	19728	149	414	4
GEN1	12.36 (0.78-196.33)	7.5E-02	10.62 (0.69-162.98)	9.0E-02	19867	10	417	1
MEN1	NA	NA	NA	NA	19874	3	418	0
MLH1	NA	NA	NA	NA	19875	2	418	0
MRE11A	NA	NA	NA	NA	19855	22	418	0
MSH2	NA	NA	NA	NA	19874	3	418	0
MSH6	NA	NA	NA	NA	19860	17	418	0
MUTYH	NA	NA	NA	NA	19858	19	418	0
NBN	NA	NA	NA	NA	19823	54	418	0
NF1	NA	NA	NA	NA	19866	11	418	0
PIK3CA	NA	NA	NA	NA	19873	4	418	0
PMS2	NA	NA	NA	NA	19863	14	418	0
PTEN	22.74 (1.15-450.24)	4.0E-02	24.95 (1.21-513.65)	3.7E-02	19873	4	417	1
RAD50	5.15 (1.68-15.79)	4.1E-03	5.00 (1.63-15.34)	5.1E-03	19820	57	413	5
RECQL	2.12 (0.23-19.34)	5.1E-01	1.96 (0.22-17.73)	5.5E-01	19850	27	417	1
RINT1	2.75 (0.28-27.25)	3.9E-01	2.86 (0.28-28.95)	3.7E-01	19860	17	417	1
STK11	NA	NA	NA	NA	19876	1	418	0
XRCC2	NA	NA	NA	NA	19872	5	418	0

Abbreviations: No. = number; CBC = contralateral breast cancer; HR = hazard ratio; CI = confidence interval; P = p-value.
Analyses included women from 32 studies with information about contralateral breast cancer diagnosis. NA: not assessable due to absence of mutation carriers with events.
Genes on the BRIDGES panel (Dorling et al., NEJM 2021) other than *ATM*, *BARD1*, *BRCA1*, *BRCA2*, *CHEK2*, *PALB2*, *RAD51C*, *RAD51D*, and *TP53* are presented here.

[a] Adjusted analyses were performed by including age at diagnosis, nodal status, size category, grade, ERB-B2 receptor tyrosine kinase 2 (*ERBB2*) status of the first breast cancer, (neo)adjuvant chemotherapy, endocrine therapy and trastuzumab as covariates in the Cox regression model.

Table S21. Association of protein-truncating variants in 25 putative breast cancer genes with risk of contralateral breast cancer in women diagnosed with ER-negative first breast cancer.

Gene	Unadjusted analyses		Adjusted analyses[a]		No. of women		No. of CBC	
	HR (95%CI)	P	HR (95%CI)	P	Non-carriers	Carriers	Non-carriers	Carriers
ABRAXAS1	NA	NA	NA	NA	5037	1	139	0
AKT1	NA	NA	NA	NA	5038	0	139	0
BABAM2	NA	NA	NA	NA	5038	0	139	0
BRIP1	5.11 (0.42-62.75)	2.0E-01	5.41 (0.42-70.24)	1.9E-01	5027	11	138	1
CDH1	NA	NA	NA	NA	5036	2	139	0
EPCAM	NA	NA	NA	NA	5037	1	139	0
FANCC	1.76 (0.20-15.18)	6.1E-01	1.59 (0.18-13.87)	6.7E-01	5025	13	138	1
FANCM	NA	NA	NA	NA	4989	49	139	0
GEN1	NA	NA	NA	NA	5034	4	139	0
MEN1	NA	NA	NA	NA	5038	0	139	0
MLH1	NA	NA	NA	NA	5037	1	139	0
MRE11A	NA	NA	NA	NA	5032	6	139	0
MSH2	NA	NA	NA	NA	5035	3	139	0
MSH6	NA	NA	NA	NA	5029	9	139	0
MUTYH	NA	NA	NA	NA	5032	6	139	0
NBN	NA	NA	NA	NA	5026	12	139	0
NF1	NA	NA	NA	NA	5034	4	139	0
PIK3CA	NA	NA	NA	NA	5038	0	139	0
PMS2	NA	NA	NA	NA	5035	3	139	0
PTEN	7.38 (0.53-101.84)	1.4E-01	3.92 (0.30-52.00)	3.0E-01	5036	2	138	1
RAD50	6.03 (0.99-36.70)	5.1E-02	6.27 (0.98-39.95)	5.2E-02	5022	16	137	2
RECQL	NA	NA	NA	NA	5032	6	139	0
RINT1	NA	NA	NA	NA	5036	2	139	0
STK11	NA	NA	NA	NA	5038	0	139	0
XRCC2	NA	NA	NA	NA	5036	2	139	0

Abbreviations: No. = number; CBC = contralateral breast cancer; HR = hazard ratio; CI = confidence interval; P = p-value.
Analyses included women from 32 studies with information about contralateral breast cancer diagnosis. NA: not assessable due to absence of mutation carriers with events.
Genes on the BRIDGES panel (Dorling et al., NEJM 2021) other than *ATM*, *BARD1*, *BRCA1*, *BRCA2*, *CHEK2*, *PALB2*, *RAD51C*, *RAD51D*, and *TP53* are presented here.

[a] Adjusted analyses were performed by including age at diagnosis, nodal status, size category, grade, ERB-B2 receptor tyrosine kinase 2 (*ERBB2*) status of the first breast cancer, (neo)adjuvant chemotherapy, endocrine therapy and trastuzumab as covariates in the Cox regression model.

Table S22. Heterogeneity test for the association of protein-truncating variants in 25 putative breast cancer genes with contralateral breast cancer risk and breast cancer-specific survival, by ER status of the first breast cancer.

Gene	Contralateral breast cancer risk		Breast cancer-specific survival	
	P	P[a]	P	P[a]
ABRAXAS1	NA	NA	NA	NA
AKT1	NA	NA	NA	NA
BABAM2	NA	NA	NA	NA
BRIP1	NA	NA	4.5E-01	2.6E-01
CDH1	NA	NA	NA	NA
EPCAM	NA	NA	NA	NA
FANCC	7.9E-01	7.9E-01	3.7E-01	3.1E-01
FANCM	NA	NA	3.2E-01	3.4E-01
GEN1	NA	NA	1.7E-02	1.3E-02
MEN1	NA	NA	NA	NA
MLH1	NA	NA	NA	NA
MRE11A	NA	NA	4.8E-01	4.8E-01
MSH2	NA	NA	5.6E-01	8.6E-01
MSH6	NA	NA	NA	NA
MUTYH	NA	NA	NA	NA
NBN	NA	NA	8.5E-01	8.0E-01
NF1	NA	NA	NA	NA
PIK3CA	NA	NA	NA	NA
PMS2	NA	NA	NA	NA
PTEN	NA	NA	NA	NA
RAD50	7.5E-01	7.5E-01	3.0E-01	6.5E-01
RECQL	NA	NA	1.4E-01	1.0E-01
RINT1	NA	NA	NA	NA
STK11	NA	NA	NA	NA
XRCC2	NA	NA	NA	NA

Abbreviation: P = p-value. Heterogeneity tests are for the hazard ratio (HR) estimates presented in Tables S20-S21 (contralateral breast cancer risk) and S34-S35 (breast cancer-specific survival) and compare a model including main effects and an interaction term between the mutation carrier status and the ER status of the first breast cancer, with a model without the interaction term. NA: not assessable within ER-positive and/or ER-negative tumors due to absence of mutation carriers or of mutation carriers with events. Genes on the BRIDGES panel (Dorling et al., NEJM 2021) other than *ATM*, *BARD1*, *BRCA1*, *BRCA2*, *CHEK2*, *PALB2*, *RAD51C*,

RAD51D, and *TP53* are presented here. [a] The two model compared additionally include the covariates specified in Tables S20-S21 and S34-S35.

Table S23. **Association of rare missense variants in 25 putative breast cancer genes with risk of contralateral breast cancer in women diagnosed with ER-positive first breast cancer.**

Gene	Unadjusted analyses		Adjusted analyses[a]		No. of women		No. of CBC	
	HR (95%CI)	P	HR (95%CI)	P	Non-carriers	Carriers	Non-carriers	Carriers
ABRAXAS1	1.55 (0.46-5.25)	4.8E-01	1.57 (0.46-5.36)	4.7E-01	19777	94	415	3
AKT1	3.46 (0.88-13.6)	7.5E-02	3.74 (0.93-15.02)	6.3E-02	19831	44	415	3
BABAM2	NA	NA	NA	NA	19810	62	418	0
BRIP1	1.14 (0.56-2.34)	7.1E-01	1.14 (0.56-2.35)	7.2E-01	19548	299	410	8
CDH1	1.24 (0.57-2.70)	5.8E-01	1.24 (0.57-2.71)	5.8E-01	19624	249	410	7
EPCAM	0.48 (0.09-2.72)	4.1E-01	0.49 (0.09-2.83)	4.3E-01	19792	80	417	1
FANCC	1.25 (0.54-2.89)	6.0E-01	1.27 (0.55-2.94)	5.8E-01	19603	246	411	6
FANCM	1.47 (0.87-2.50)	1.5E-01	1.46 (0.86-2.49)	1.6E-01	19171	557	398	16
GEN1	0.19 (0.04-0.78)	2.1E-02	0.18 (0.04-0.75)	1.9E-02	19622	245	416	1
MEN1	NA	NA	NA	NA	19822	52	418	0
MLH1	1.22 (0.56-2.63)	6.2E-01	1.26 (0.58-2.75)	5.6E-01	19614	261	411	7
MRE11A	1.46 (0.62-3.44)	3.9E-01	1.51 (0.64-3.59)	3.5E-01	19639	216	412	6
MSH2	0.67 (0.29-1.54)	3.4E-01	0.68 (0.29-1.59)	3.7E-01	19550	324	413	5
MSH6	1.38 (0.75-2.52)	3.0E-01	1.35 (0.74-2.47)	3.3E-01	19456	404	406	12
MUTYH	0.65 (0.23-1.87)	4.2E-01	0.64 (0.22-1.85)	4.1E-01	19644	214	415	3
NBN	1.85 (0.86-4.00)	1.2E-01	1.87 (0.86-4.06)	1.1E-01	19602	221	410	8
NF1	1.18 (0.58-2.43)	6.5E-01	1.24 (0.60-2.56)	5.7E-01	19533	333	410	8
PIK3CA	1.08 (0.26-4.39)	9.2E-01	1.04 (0.25-4.22)	9.6E-01	19790	83	416	2
PMS2	1.66 (0.87-3.17)	1.3E-01	1.67 (0.87-3.20)	1.2E-01	19507	356	407	11
PTEN	NA	NA	NA	NA	19834	39	417	0
RAD50	1.36 (0.76-2.42)	3.0E-01	1.35 (0.75-2.43)	3.1E-01	19389	431	400	13
RECQL	0.21 (0.05-0.91)	3.7E-02	0.21 (0.05-0.94)	4.1E-02	19624	226	416	1
RINT1	0.80 (0.34-1.89)	6.2E-01	0.78 (0.33-1.82)	5.6E-01	19566	294	412	5
STK11	1.60 (0.19-13.29)	6.6E-01	1.64 (0.19-13.80)	6.5E-01	19839	37	417	1
XRCC2	2.28 (0.74-6.98)	1.5E-01	2.35 (0.76-7.27)	1.4E-01	19790	82	414	4

Abbreviations: No. = number; CBC = contralateral breast cancer; HR = hazard ratio; CI = confidence interval; P = p-value.
Analyses included women from 32 studies with information about contralateral breast cancer diagnosis. NA: not assessable due to absence of mutation carriers with events. Genes on the BRIDGES panel (Dorling et al., NEJM 2021) other than *ATM*, *BARD1*, *BRCA1*, *BRCA2*, *CHEK2*, *PALB2*, *RAD51C*, *RAD51D*, and *TP53* are presented here.
[a] Adjusted analyses were performed by including age at diagnosis, nodal status, size category, grade, ERB-B2 receptor tyrosine kinase 2 (*ERBB2*) status of the first breast cancer, (neo)adjuvant chemotherapy, endocrine therapy and trastuzumab as covariates in the Cox regression model. The analysis for each gene excluded carriers of protein-truncating variants in that gene.

Table S24. Association of rare missense variants in 25 putative breast cancer genes with risk of contralateral breast cancer in women diagnosed with ER-negative first breast cancer.

Gene	Unadjusted analyses		Adjusted analyses[a]		No. of women		No. of CBC	
	HR (95%CI)	P	HR (95%CI)	P	Non-carriers	Carriers	Non-carriers	Carriers
ABRAXAS1	NA	NA	NA	NA	5021	16	139	0
AKT1	2.14 (0.23-19.70)	5.0E-01	2.29 (0.24-22.21)	4.7E-01	5021	17	138	1
BABAM2	NA	NA	NA	NA	5020	18	139	0
BRIP1	0.34 (0.07-1.80)	2.1E-01	0.33 (0.06-1.73)	1.9E-01	4935	92	137	1
CDH1	0.87 (0.13-5.98)	8.9E-01	0.83 (0.12-5.81)	8.5E-01	4990	46	138	1
EPCAM	4.08 (1.00-16.67)	5.0E-02	4.24 (1.00-18.00)	5.0E-02	5009	28	136	3
FANCC	NA	NA	NA	NA	4960	65	138	0
FANCM	0.63 (0.22-1.83)	3.9E-01	0.68 (0.23-2.03)	4.9E-01	4830	159	136	3
GEN1	0.51 (0.09-2.99)	4.6E-01	0.47 (0.08-2.72)	3.9E-01	4973	61	138	1
MEN1	3.76 (0.33-42.79)	2.9E-01	4.52 (0.36-56.4)	2.4E-01	5028	10	138	1
MLH1	0.77 (0.20-2.96)	7.0E-01	0.81 (0.20-3.19)	7.6E-01	4958	79	137	2
MRE11A	1.23 (0.29-5.29)	7.8E-01	1.27 (0.29-5.68)	7.5E-01	4975	57	137	2
MSH2	NA	NA	NA	NA	4971	64	139	0
MSH6	0.38 (0.07-2.02)	2.6E-01	0.37 (0.07-1.96)	2.4E-01	4936	93	138	1
MUTYH	0.86 (0.12-5.88)	8.8E-01	0.85 (0.12-6.04)	8.7E-01	4968	64	138	1
NBN	1.70 (0.49-5.92)	4.0E-01	1.85 (0.51-6.66)	3.5E-01	4958	68	136	3
NF1	1.86 (0.53-6.58)	3.3E-01	1.92 (0.53-6.98)	3.2E-01	4957	77	136	3
PIK3CA	NA	NA	NA	NA	5018	20	139	0
PMS2	1.53 (0.53-4.45)	4.3E-01	1.56 (0.53-4.64)	4.2E-01	4934	101	135	4
PTEN	NA	NA	NA	NA	5028	8	138	0
RAD50	0.77 (0.20-2.95)	7.0E-01	0.81 (0.20-3.20)	7.6E-01	4939	83	135	2
RECQL	2.36 (0.76-7.35)	1.4E-01	2.55 (0.79-8.20)	1.2E-01	4976	56	135	4
RINT1	1.57 (0.54-4.58)	4.1E-01	1.40 (0.48-4.09)	5.3E-01	4945	91	135	4
STK11	NA	NA	NA	NA	5032	6	139	0
XRCC2	3.94 (0.71-22.04)	1.2E-01	4.77 (0.80-28.49)	8.6E-02	5014	22	137	2

Abbreviations: No. = number; CBC = contralateral breast cancer; HR = hazard ratio; CI = confidence interval; P = p-value.
Analyses included women from 32 studies with information about contralateral breast cancer diagnosis. NA: not assessable due to absence of mutation carriers with events. Genes on the BRIDGES panel (Dorling et al., NEJM 2021) other than *ATM*, *BARD1*, *BRCA1*, *BRCA2*, *CHEK2*, *PALB2*, *RAD51C*, *RAD51D*, and *TP53* are presented here.
[a] Adjusted analyses were performed by including age at diagnosis, nodal status, size category, grade, ERB-B2 receptor tyrosine kinase 2 (*ERBB2*) status of the first breast cancer, (neo)adjuvant chemotherapy, endocrine therapy and trastuzumab as covariates in the Cox regression model. The analysis for each gene excluded carriers of protein-truncating variants in that gene.

Table S25. Heterogeneity test for the association of rare missense variants in 25 putative breast cancer genes with contralateral breast cancer risk and breast cancer-specific survival, by ER status of the first breast cancer.

Gene	Contralateral breast cancer risk		Breast cancer-specific survival	
	P	P[a]	P	P[a]
ABRAXAS1	NA	NA	9.5E-01	8.5E-01
AKT1	6.9E-01	6.4E-01	5.4E-01	3.1E-01
BABAM2	NA	NA	4.9E-02	4.9E-02
BRIP1	3.1E-01	3.5E-01	8.4E-01	7.8E-01
CDH1	6.1E-01	6.2E-01	3.2E-01	6.1E-01
EPCAM	4.3E-02	6.6E-02	2.1E-01	4.1E-01
FANCC	NA	NA	1.7E-01	2.0E-01
FANCM	1.6E-01	2.2E-01	1.2E-01	2.4E-01
GEN1	5.3E-01	5.4E-01	2.9E-01	1.8E-01
MEN1	NA	NA	5.5E-01	8.9E-01
MLH1	7.0E-01	7.3E-01	9.7E-01	8.2E-01
MRE11A	7.9E-01	8.0E-01	3.2E-01	3.5E-01
MSH2	NA	NA	2.0E-01	4.1E-01
MSH6	1.5E-01	2.4E-01	7.2E-01	9.8E-01
MUTYH	7.7E-01	7.2E-01	3.2E-01	5.3E-01
NBN	8.5E-01	9.0E-01	3.2E-01	4.2E-01
NF1	4.5E-01	4.5E-01	8.7E-02	4.5E-02
PIK3CA	NA	NA	9.2E-01	9.1E-01
PMS2	8.8E-01	9.2E-01	6.0E-01	7.5E-01
PTEN	NA	NA	6.9E-01	8.8E-01
RAD50	3.1E-01	3.5E-01	9.7E-01	5.1E-01
RECQL	1.6E-02	3.0E-02	1.8E-01	1.6E-01
RINT1	2.3E-01	2.4E-01	5.0E-02	6.2E-02
STK11	NA	NA	1.2E-01	2.5E-01
XRCC2	4.2E-01	3.2E-01	3.8E-02	3.6E-02

Abbreviation: P = p-value. Heterogeneity tests are for the hazard ratio (HR) estimates presented in Tables S23-S24 (contralateral breast cancer risk) and S37-S38 (breast cancer-specific survival) and compare a model including main effects and an interaction term between the mutation carrier status and the ER status of the first breast cancer, with a model without the interaction term. NA: not assessable within ER-positive and/or ER-negative tumors due to absence of mutation carriers or of mutation carriers with events. Genes on the BRIDGES panel (Dorling et al., NEJM 2021) other than *ATM*, *BARD1*, *BRCA1*, *BRCA2*, *CHEK2*, *PALB2*, *RAD51C*,*RAD51D*, and *TP53* are presented here.

[a] The two model compared additionally include the covariates specified in Tables S23-S24 and S37-S38.

Table S26. **Association of protein-truncating variants in 9 breast cancer genes and of pathogenic/likely pathogenic rare missense variants in *BRCA1*, *BRCA2* and *TP53* with breast cancer-specific survival in women diagnosed with ER-positive first breast cancer.**

Gene	Unadjusted analyses		Adjusted analyses[a]		No. of women		No. of BC deaths	
PTVs (unless indicated otherwise)	**HR (95%CI)**	**P**	**HR (95%CI)**	**P**	**Non-carriers**	**Carriers**	**Non-carriers**	**Carriers**
ATM	1.37 (0.83-2.27)	2.2E-01	1.08 (0.66-1.76)	7.6E-01	22429	161	1980	17
BARD1	1.12 (0.27-4.59)	8.8E-01	1.69 (0.37-7.71)	5.0E-01	22567	23	1995	2
BRCA1[b]	**1.87 (1.00-3.51)**	**5.0E-02**	1.60 (0.86-2.97)	1.4E-01	22505	85	1985	12
BRCA2[b]	**2.14 (1.57-2.93)**	**1.7E-06**	**1.53 (1.13-2.07)**	**5.4E-03**	22299	291	1946	51
CHEK2	**1.62 (1.25-2.10)**	**2.4E-04**	**1.46 (1.13-1.89)**	**3.9E-03**	22089	501	1927	70
c.1100delC	**1.73 (1.31-2.29)**	**1.1E-04**	**1.55 (1.18-2.05)**	**1.9E-03**	22089	408	1927	61
Other	1.14 (0.58-2.23)	7.0E-01	1.04 (0.54-2.02)	9.1E-01	22089	93	1927	9
PALB2	**2.02 (1.26-3.23)**	**3.3E-03**	1.50 (0.96-2.36)	7.8E-02	22458	132	1975	22
RAD51C	NA	NA	NA	NA	22571	19	1997	0
RAD51D	0.71 (0.11-4.49)	7.1E-01	0.71 (0.11-4.51)	7.1E-01	22578	12	1996	1
TP53[b]	**2.86 (1.02-8.02)**	**4.6E-02**	1.92 (0.72-5.12)	1.9E-01	22559	31	1992	5

Abbreviations: No. = number; BC = breast cancer; PTVs = protein-truncating variants; HR = hazard ratio; CI = confidence interval; P = p-value.

Analyses included women from 34 studies listed in Table S1. Women who developed a CBC before study entry are excluded. Statistically significant associations (P<5E-02) are highlighted in bold. NA: not assessable due to absence of mutation carriers with events.

[a]Adjusted analyses were performed by including age at diagnosis, nodal status, size category, grade, ERB-B2 receptor tyrosine kinase 2 (*ERBB2*) status of the first breast cancer, (neo)adjuvant chemotherapy, endocrine therapy and trastuzumab as covariates in the Cox regression model.

[b] Combined PTVs and rare pathogenic/likely pathogenic missense variants as defined in Dorling et al. (NEJM 2021).

Table S27. **Association of protein-truncating variants in 9 breast cancer genes and of pathogenic/likely pathogenic rare missense variants in *BRCA1*, *BRCA2* and *TP53* with breast cancer-specific survival in women diagnosed with ER-negative first breast cancer.**

Gene	Unadjusted analyses		Adjusted analyses[a]		No. of women		No. of BC deaths	
PTVs (unless indicated otherwise)	**HR (95%CI)**	**P**	**HR (95%CI)**	**P**	**Non-carriers**	**Carriers**	**Non-carriers**	**Carriers**
ATM	0.90 (0.34-2.40)	8.4E-01	0.77 (0.30-2.02)	6.0E-01	5642	23	830	4
BARD1	0.73 (0.19-2.71)	6.4E-01	0.58 (0.16-2.09)	4.1E-01	5644	21	832	2
BRCA1[b]	**0.66 (0.44-0.99)**	**4.3E-02**	0.72 (0.48-1.09)	1.2E-01	5447	218	812	22
BRCA2[b]	0.74 (0.43-1.26)	2.7E-01	0.76 (0.44-1.31)	3.2E-01	5566	99	822	12
CHEK2	1.32 (0.77-2.25)	3.1E-01	1.15 (0.67-1.95)	6.1E-01	5589	76	819	15
c.1100delC	1.24 (0.67-2.30)	5.0E-01	1.17 (0.63-2.19)	6.1E-01	5589	57	819	11
Other	1.58 (0.55-4.56)	4.0E-01	1.08 (0.39-2.95)	8.9E-01	5589	19	819	4
PALB2	1.29 (0.65-2.56)	4.7E-01	1.26 (0.63-2.50)	5.1E-01	5617	48	825	9
RAD51C	1.34 (0.41-4.41)	6.3E-01	1.41 (0.41-4.83)	5.8E-01	5653	12	831	3
RAD51D	0.82 (0.21-3.13)	7.7E-01	0.70 (0.19-2.62)	6.0E-01	5654	11	832	2
TP53[b]	0.73 (0.11-4.70)	7.4E-01	1.06 (0.14-7.77)	9.6E-01	5655	10	833	1

Abbreviations: No. = number; BC = breast cancer; PTVs = protein-truncating variants; HR = hazard ratio; CI = confidence interval; P = p-value.

Analyses included women from 34 studies listed in Table S1. Women who developed a CBC before study entry are excluded. Statistically significant associations (P<5E-02) are highlighted in bold.

[a] Adjusted analyses were performed by including age at diagnosis, nodal status, size category, grade, ERB-B2 receptor tyrosine kinase 2 (*ERBB2*) status of the first breast cancer, (neo)adjuvant chemotherapy, endocrine therapy and trastuzumab as covariates in the Cox regression model.

[b] Combined PTVs and rare pathogenic/likely pathogenic missense variants as defined in Dorling et al. (NEJM 2021).

Table S28. **Association of rare missense variants in 9 breast cancer genes with breast cancer-specific survival.**

Gene	Unadjusted analyses		Adjusted analyses[a]		No. of women		No. of BC deaths	
	HR (95%CI)	P	HR (95%CI)	P	Non-carriers	Carriers	Non-carriers	Carriers
ATM	1.00 (0.85-1.16)	9.6E-01	0.98 (0.84-1.14)	7.8E-01	32411	1740	3248	173
BARD1	1.17 (0.87-1.59)	3.0E-01	1.15 (0.85-1.55)	3.7E-01	33944	403	3399	45
BRCA1	1.14 (0.93-1.39)	2.0E-01	1.13 (0.92-1.38)	2.4E-01	33160	921	3307	103
BRCA2	1.05 (0.90-1.21)	5.5E-01	1.01 (0.87-1.18)	8.5E-01	32116	1833	3190	189
CHEK2	1.27 (1.00-1.62)	5.1E-02	1.23 (0.97-1.57)	9.4E-02	33091	611	3277	72
PALB2	1.11 (0.84-1.48)	4.6E-01	1.09 (0.82-1.45)	5.6E-01	33735	442	3365	49
RAD51C	1.17 (0.69-1.96)	5.6E-01	1.19 (0.70-2.00)	5.2E-01	34223	138	3431	15
RAD51D	0.80 (0.42-1.50)	4.8E-01	0.74 (0.40-1.39)	3.5E-01	34256	114	3434	9
TP53	**1.84 (1.26-2.70)**	**1.8E-03**	**1.63 (1.11-2.38)**	**1.2E-02**	34218	179	3416	32

Abbreviations: No. = number; BC = breast cancer; HR = hazard ratio; CI = confidence interval; P = p-value.
Analyses included women from 34 studies listed in Table S1. Women who developed a CBC before study entry are excluded. The analysis for each gene excluded carriers of protein-truncating variants in that gene. Statistically significant associations (P<5E-02) are highlighted in bold.
[a]Adjusted analyses were performed by including age at diagnosis, nodal status, size category, grade, estrogen receptor (ER) status, ERB-B2 receptor tyrosine kinase 2 (*ERBB2*) status of the first breast cancer, (neo)adjuvant chemotherapy, endocrine therapy and trastuzumab as covariates in the Cox regression model.

Table S29. **Association of rare missense variants in 9 breast cancer genes with breast cancer-specific survival in women diagnosed with ER-positive first breast cancer.**

Gene	Unadjusted analyses		Adjusted analyses[a]		No. of women		No. of BC deaths	
	HR (95%CI)	P	HR (95%CI)	P	Non-carriers	Carriers	Non-carriers	Carriers
ATM	1.11 (0.91-1.35)	3.1E-01	1.05 (0.87-1.28)	6.0E-01	21275	1154	1870	110
BARD1	1.10 (0.73-1.66)	6.4E-01	1.04 (0.69-1.56)	8.6E-01	22301	266	1971	24
BRCA1	1.10 (0.84-1.43)	4.9E-01	1.10 (0.84-1.44)	4.8E-01	21920	595	1928	58
BRCA2	1.00 (0.82-1.22)	9.8E-01	1.00 (0.82-1.23)	9.8E-01	21144	1174	1847	102
CHEK2	**1.44 (1.07-1.96)**	**1.8E-02**	1.33 (0.98-1.80)	6.5E-02	21665	424	1879	48
PALB2	1.14 (0.79-1.64)	4.8E-01	1.10 (0.76-1.57)	6.2E-01	22152	306	1944	31
RAD51C	1.11 (0.55-2.25)	7.7E-01	1.17 (0.57-2.39)	6.7E-01	22488	83	1989	8
RAD51D	0.83 (0.36-1.95)	6.7E-01	0.75 (0.32-1.73)	5.0E-01	22505	73	1991	5
TP53	**2.06 (1.26-3.37)**	**4.0E-03**	**1.64 (1.01-2.64)**	**4.4E-02**	22470	119	1977	20

Abbreviations: No. = number; BC = breast cancer; HR = hazard ratio; CI = confidence interval; P = p-value.
Analyses included women from 34 studies listed in Table S1. Women who developed a CBC before study entry are excluded. The analysis for each gene excluded carriers of protein-truncating variants in that gene. Statistically significant associations after (P<5E-02) are highlighted in bold.
[a]Adjusted analyses were performed by including age at diagnosis, nodal status, size category, grade, ERB-B2 receptor tyrosine kinase 2 (*ERBB2*) status of the first breast cancer, (neo)adjuvant chemotherapy, endocrine therapy and trastuzumab as covariates in the Cox regression model.

Table S30. **Association of rare missense variants in 9 breast cancer genes with breast cancer-specific survival in women diagnosed with ER-negative first breast cancer.**

Gene	Unadjusted analyses		Adjusted analyses[a]		No. of women		No. of BC deaths	
	HR (95%CI)	P	HR (95%CI)	P	Non-carriers	Carriers	Non-carriers	Carriers
ATM	0.93 (0.68-1.27)	6.4E-01	0.88 (0.64-1.20)	4.2E-01	5357	285	789	41
BARD1	0.81 (0.43-1.53)	5.1E-01	0.87 (0.45-1.65)	6.6E-01	5571	73	823	9
BRCA1	1.21 (0.83-1.76)	3.3E-01	1.21 (0.83-1.77)	3.3E-01	5302	172	784	30
BRCA2	1.13 (0.86-1.50)	3.9E-01	1.05 (0.79-1.39)	7.4E-01	5241	332	770	55
CHEK2	1.11 (0.59-2.10)	7.5E-01	0.96 (0.51-1.81)	9.1E-01	5522	67	809	10
PALB2	0.88 (0.46-1.67)	7.0E-01	0.82 (0.43-1.56)	5.5E-01	5550	67	816	9
RAD51C	1.02 (0.37-2.76)	9.7E-01	1.02 (0.37-2.82)	9.7E-01	5622	31	827	4
RAD51D	0.59 (0.17-2.11)	4.2E-01	0.64 (0.17-2.33)	5.0E-01	5632	22	830	2
TP53	1.05 (0.47-2.37)	9.0E-01	1.15 (0.50-2.64)	7.3E-01	5629	33	827	6

Abbreviations: No. = number; BC = breast cancer; HR = hazard ratio; CI = confidence interval; P = p-value.
Analyses included women from 34 studies listed in Table S1. Women who developed a CBC before study entry are excluded. The analysis for each gene excluded carriers of protein-truncating variants in that gene.
[a] Adjusted analyses were performed by including age at diagnosis, nodal status, size category, grade, ERB-B2 receptor tyrosine kinase 2 (*ERBB2*) status of the first breast cancer, (neo)adjuvant chemotherapy, endocrine therapy and trastuzumab as covariates in the Cox regression model.

Table S31. Sensitivity analysis for the association of protein-truncating variants in 9 breast cancer genes and of pathogenic/likely pathogenic rare missense variants in *BRCA1*, *BRCA2* and *TP53* with breast cancer-specific survival in women from population- and hospital-based studies plus women without family history from studies including women with family history of breast cancer.

Gene	Unadjusted analyses		Adjusted analyses[a]		No. of women		No. of BC deaths	
PTVs (unless indicated otherwise)	**HR (95%CI)**	**P**	**HR (95%CI)**	**P**	**Non-carriers**	**Carriers**	**Non-carriers**	**Carriers**
ATM	1.20 (0.78-1.83)	4.1E-01	1.08 (0.71-1.64)	7.3E-01	30022	200	3068	23
BARD1	1.05 (0.39-2.83)	9.2E-01	0.79 (0.31-2.04)	6.3E-01	30178	44	3087	4
BRCA1[b]	1.27 (0.92-1.75)	1.5E-01	0.89 (0.66-1.22)	4.8E-01	29879	343	3050	41
BRCA2[b]	**1.62 (1.27-2.08)**	**1.3E-04**	1.24 (0.98-1.58)	7.7E-02	29767	455	3016	75
CHEK2	**1.38 (1.09-1.76)**	**8.4E-03**	1.27 (1.00-1.61)	5.1E-02	29676	546	3016	75
c.1100delC	**1.41 (1.07-1.84)**	**1.3E-02**	**1.35 (1.03-1.76)**	**3.0E-02**	29676	429	3016	60
Other	1.30 (0.77-2.21)	3.3E-01	1.03 (0.62-1.72)	9.0E-01	29676	117	3016	15
PALB2	**1.71 (1.15-2.53)**	**7.3E-03**	1.36 (0.93-1.98)	1.2E-01	30044	178	3061	30
RAD51C	0.71 (0.19-2.63)	6.1E-01	0.68 (0.18-2.52)	5.6E-01	30193	29	3089	2
RAD51D	1.36 (0.54-3.43)	5.1E-01	0.85 (0.36-2.00)	7.0E-01	30195	27	3086	5
TP53[b]	**2.73 (1.15-6.47)**	**2.3E-02**	2.17 (0.93-5.07)	7.4E-02	30194	28	3084	7

Abbreviations: No. = number; BC = breast cancer; PTVs = protein-truncating variants; HR = hazard ratio; CI = confidence interval; P = p-value.

Women who developed a CBC before study entry are excluded. Statistically significant associations (P<5E-02) are highlighted in bold.

[a]Adjusted analyses were performed by including age at diagnosis, nodal status, size category, grade, estrogen receptor (ER) status, ERB-B2 receptor tyrosine kinase 2 (*ERBB2*) status of the first breast cancer, (neo)adjuvant chemotherapy, endocrine therapy and trastuzumab as covariates in the Cox regression model.

[b] Combined PTVs and rare pathogenic/likely pathogenic missense variants as defined in Dorling et al. (NEJM 2021).

Table S32. Sensitivity analysis for the association of rare missense variants in 9 breast cancer genes with breast cancer-specific survival in women from population- and hospital-based studies plus women without family history from studies including women with family history of breast cancer.

Gene	Unadjusted analyses		Adjusted analyses[a]		No. of women		No. BC deaths	
	HR (95%CI)	P	HR (95%CI)	P	Non-carriers	Carriers	Non-carriers	Carriers
ATM	1.02 (0.87-1.21)	7.8E-01	0.99 (0.84-1.17)	9.0E-01	28553	1469	2914	154
BARD1	1.14 (0.82-1.57)	4.3E-01	1.12 (0.81-1.55)	4.8E-01	29827	351	3048	39
BRCA1	1.11 (0.90-1.38)	3.2E-01	1.12 (0.90-1.38)	3.2E-01	29111	810	2963	90
BRCA2	1.05 (0.90-1.23)	5.6E-01	1.00 (0.86-1.17)	9.8E-01	28203	1591	2854	167
CHEK2	1.26 (0.97-1.63)	8.5E-02	1.20 (0.92-1.55)	1.8E-01	29171	505	2954	62
PALB2	1.18 (0.88-1.59)	2.7E-01	1.13 (0.84-1.52)	4.0E-01	29657	387	3014	47
RAD51C	1.02 (0.58-1.81)	9.3E-01	1.10 (0.62-1.96)	7.4E-01	30078	115	3077	12
RAD51D	0.88 (0.46-1.67)	7.0E-01	0.82 (0.44-1.56)	5.5E-01	30097	98	3077	9
TP53	**1.98 (1.32-2.98)**	**9.8E-04**	**1.68 (1.12-2.50)**	**1.1E-02**	30080	139	3061	29

Abbreviations: No. = number; BC = breast cancer; HR = hazard ratio; CI = confidence interval; P = p-value.
Women who developed a CBC before study entry are excluded. The analysis for each gene excluded carriers of protein-truncating variants in that gene. Statistically significant associations (P<5E-02) are highlighted in bold.
[a] Adjusted analyses were performed by including age at diagnosis, nodal status, size category, grade, estrogen receptor (ER) status, ERB-B2 receptor tyrosine kinase 2 (*ERBB2*) status of the first breast cancer, (neo)adjuvant chemotherapy, endocrine therapy and trastuzumab as covariates in the Cox regression model.

Table S33. Association of protein-truncating variants in 25 putative breast cancer genes with breast cancer-specific survival.

Gene	Unadjusted analyses		Adjusted analyses[a]		No. of women		No. of BC deaths	
	HR (95%CI)	P	HR (95%CI)	P	Non-carriers	Carriers	Non-carriers	Carriers
ABRAXAS1	0.66 (0.11-4.14)	6.6E-01	0.79 (0.12-5.31)	8.1E-01	34389	12	3448	1
AKT1	NA	NA	NA	NA	34398	3	3449	0
BABAM2	5.01 (1.20-21.03)	2.8E-02	7.74 (1.67-35.84)	8.8E-03	34394	7	3446	3
BRIP1	1.88 (0.97-3.61)	6.0E-02	1.89 (0.97-3.67)	6.0E-02	34341	60	3438	11
CDH1	NA	NA	NA	NA	34395	6	3449	0
EPCAM	NA	NA	NA	NA	34393	8	3449	0
FANCC	0.79 (0.34-1.83)	5.8E-01	0.84 (0.36-1.99)	7.0E-01	34342	59	3444	5
FANCM	1.45 (1.03-2.06)	3.6E-02	1.33 (0.94-1.88)	1.1E-01	34139	262	3413	36
GEN1	2.73 (1.07-6.93)	3.5E-02	2.15 (0.86-5.35)	1.0E-01	34379	22	3443	6
MEN1	NA	NA	NA	NA	34398	3	3449	0
MLH1	NA	NA	NA	NA	34398	3	3449	0
MRE11A	1.14 (0.42-3.09)	8.0E-01	1.46 (0.51-4.15)	4.8E-01	34366	35	3445	4
MSH2	2.63 (0.71-9.78)	1.5E-01	3.09 (0.77-12.33)	1.1E-01	34390	11	3446	3
MSH6	0.38 (0.07-1.96)	2.5E-01	0.31 (0.06-1.48)	1.4E-01	34373	28	3448	1
MUTYH	0.43 (0.08-2.35)	3.3E-01	0.48 (0.08-2.68)	4.0E-01	34372	29	3448	1
NBN	1.20 (0.61-2.37)	5.9E-01	0.95 (0.50-1.83)	8.8E-01	34318	83	3440	9
NF1	0.94 (0.24-3.73)	9.3E-01	0.93 (0.24-3.68)	9.2E-01	34381	20	3447	2
PIK3CA	NA	NA	NA	NA	34395	6	3449	0
PMS2	1.50 (0.53-4.26)	4.5E-01	1.06 (0.39-2.86)	9.1E-01	34374	27	3445	4
PTEN	NA	NA	NA	NA	34386	15	3449	0
RAD50	1.08 (0.55-2.09)	8.3E-01	1.24 (0.63-2.44)	5.4E-01	34305	96	3440	9
RECQL	1.37 (0.54-3.45)	5.0E-01	1.66 (0.64-4.32)	3.0E-01	34358	43	3444	5
RINT1	0.52 (0.15-1.88)	3.2E-01	0.72 (0.19-2.77)	6.4E-01	34376	25	3447	2
STK11	NA	NA	NA	NA	34399	2	3449	0
XRCC2	1.17 (0.16-8.73)	8.8E-01	1.14 (0.15-8.61)	9.0E-01	34391	10	3448	1

Abbreviations: No. = number; BC = breast cancer; HR = hazard ratio; CI = confidence interval; P = p-value.

Analyses included women from 34 studies listed in Table S1. Women who developed a CBC before study entry are excluded. NA: not assessable due to absence of mutation carriers with events.

Genes on the BRIDGES panel (Dorling et al., NEJM 2021) other than *ATM*, *BARD1*, *BRCA1*, *BRCA2*, *CHEK2*, *PALB2*, *RAD51C*, *RAD51D*, and *TP53* are presented here.

[a] Adjusted analyses were performed by including age at diagnosis, nodal status, size category, grade, estrogen receptor (ER) status, ERB-B2 receptor tyrosine kinase 2 (*ERBB2*) status of the first breast cancer, (neo)adjuvant chemotherapy, endocrine therapy and trastuzumab as covariates in the Cox regression model.

Table S34. Association of protein-truncating variants in 25 putative breast cancer genes with breast cancer-specific survival in women diagnosed with ER-positive first breast cancer.

Gene	Unadjusted analyses		Adjusted analyses[a]		No. of women		No. of BC deaths	
	HR (95%CI)	P	HR (95%CI)	P	Non-carriers	Carriers	Non-carriers	Carriers
ABRAXAS1	NA	NA	NA	NA	22584	6	1997	0
AKT1	NA	NA	NA	NA	22587	3	1997	0
BABAM2	6.91 (1.56-30.71)	1.1E-02	10.07 (2.11-47.97)	3.7E-03	22585	5	1994	3
BRIP1	2.13 (0.86-5.24)	1.0E-01	2.05 (0.83-5.08)	1.2E-01	22559	31	1991	6
CDH1	NA	NA	NA	NA	22586	4	1997	0
EPCAM	NA	NA	NA	NA	22584	6	1997	0
FANCC	0.36 (0.07-1.84)	2.2E-01	0.39 (0.07-2.07)	2.7E-01	22557	33	1996	1
FANCM	1.47 (0.93-2.32)	1.0E-01	1.31 (0.84-2.07)	2.4E-01	22432	158	1976	21
GEN1	1.65 (0.37-7.40)	5.2E-01	1.30 (0.30-5.57)	7.2E-01	22577	13	1995	2
MEN1	NA	NA	NA	NA	22587	3	1997	0
MLH1	NA	NA	NA	NA	22588	2	1997	0
MRE11A	1.63 (0.48-5.54)	4.4E-01	2.31 (0.63-8.40)	2.1E-01	22567	23	1994	3
MSH2	2.87 (0.29-28.72)	3.7E-01	2.36 (0.25-22.3)	4.5E-01	22585	5	1996	1
MSH6	0.68 (0.11-4.29)	6.9E-01	0.62 (0.10-3.82)	6.1E-01	22572	18	1996	1
MUTYH	NA	NA	NA	NA	22569	21	1997	0
NBN	1.04 (0.43-2.53)	9.2E-01	0.93 (0.39-2.24)	8.8E-01	22528	62	1992	5
NF1	0.70 (0.11-4.43)	7.0E-01	0.71 (0.11-4.58)	7.2E-01	22578	12	1996	1
PIK3CA	NA	NA	NA	NA	22586	4	1997	0
PMS2	NA	NA	NA	NA	22571	19	1997	0
PTEN	NA	NA	NA	NA	22583	7	1997	0
RAD50	1.10 (0.45-2.67)	8.4E-01	1.14 (0.46-2.81)	7.8E-01	22531	59	1992	5
RECQL	1.25 (0.38-4.03)	7.1E-01	1.24 (0.38-4.04)	7.2E-01	22560	30	1994	3
RINT1	0.92 (0.22-3.83)	9.1E-01	1.28 (0.29-5.56)	7.4E-01	22572	18	1995	2
STK11	NA	NA	NA	NA	22589	1	1997	0
XRCC2	NA	NA	NA	NA	22585	5	1997	0

Abbreviations: No. = number; BC = breast cancer; HR = hazard ratio; CI = confidence interval; P = p-value.

Analyses included women from 34 studies listed in Table S1. Women who developed a CBC before study entry are excluded. NA: not assessable due to absence of mutation carriers with events. Genes on the BRIDGES panel (Dorling et al., NEJM 2021) other than *ATM*, *BARD1*, *BRCA1*, *BRCA2*, *CHEK2*, *PALB2*, *RAD51C*, *RAD51D*, and *TP53* are presented here.

[a] Adjusted analyses were performed by including age at diagnosis, nodal status, size category, grade, ERB-B2 receptor tyrosine kinase 2 (*ERBB2*) status of the first breast cancer, (neo)adjuvant chemotherapy, endocrine therapy and trastuzumab as covariates in the Cox regression model.

Table S35. Association of protein-truncating variants in 25 putative breast cancer genes with breast cancer-specific survival in women diagnosed with ER-negative first breast cancer.

Gene	Unadjusted analyses		Adjusted analyses[a]		No. of women		No. of BC deaths	
	HR (95%CI)	P	HR (95%CI)	P	Non-carriers	Carriers	Non-carriers	Carriers
ABRAXAS1	NA	NA	NA	NA	5663	2	834	0
AKT1	NA	NA	NA	NA	5665	0	834	0
BABAM2	NA	NA	NA	NA	5665	0	834	0
BRIP1	3.51 (1.06-11.60)	4.0E-02	4.97 (1.42-17.43)	1.2E-02	5653	12	830	4
CDH1	NA	NA	NA	NA	5663	2	834	0
EPCAM	NA	NA	NA	NA	5664	1	834	0
FANCC	0.98 (0.32-3.05)	9.8E-01	1.31 (0.39-4.34)	6.6E-01	5648	17	831	3
FANCM	0.89 (0.43-1.84)	7.5E-01	0.82 (0.39-1.69)	5.9E-01	5609	56	827	7
GEN1	**8.79 (2.32-33.31)**	**1.4E-03**	7.41 (1.99-27.66)	2.9E-03	5660	5	830	4
MEN1	NA	NA	NA	NA	5665	0	834	0
MLH1	NA	NA	NA	NA	5664	1	834	0
MRE11A	0.76 (0.12-4.92)	7.7E-01	0.80 (0.12-5.38)	8.2E-01	5657	8	833	1
MSH2	1.40 (0.18-11.10)	7.5E-01	2.74 (0.26-29.39)	4.0E-01	5662	3	833	1
MSH6	NA	NA	NA	NA	5656	9	834	0
MUTYH	1.84 (0.21-16.06)	5.8E-01	1.65 (0.19-14.07)	6.5E-01	5659	6	833	1
NBN	1.32 (0.40-4.33)	6.5E-01	0.91 (0.30-2.80)	8.7E-01	5650	15	831	3
NF1	NA	NA	NA	NA	5661	4	834	0
PIK3CA	NA	NA	NA	NA	5665	0	834	0
PMS2	1.86 (0.21-16.23)	5.8E-01	2.92 (0.29-29.74)	3.6E-01	5662	3	833	1
PTEN	NA	NA	NA	NA	5663	2	834	0
RAD50	0.42 (0.08-2.29)	3.2E-01	0.64 (0.10- 4.00)	6.4E-01	5647	18	833	1
RECQL	4.64 (0.82-26.45)	8.4E-02	4.34 (0.76-24.73)	9.8E-02	5658	7	832	2
RINT1	NA	NA	NA	NA	5663	2	834	0
STK11	NA	NA	NA	NA	5665	0	834	0
XRCC2	2.40 (0.25-22.82)	4.5E-01	2.00 (0.21-19.33)	5.5E-01	5661	4	833	1

Abbreviations: No. = number; BC = breast cancer; HR = hazard ratio; CI = confidence interval; P = p-value.
Analyses included women from 34 studies listed in Table S1. Women who developed a CBC before study entry are excluded. Statistically significant associations after Bonferroni correction for 25 tests (P<2E-03) are highlighted in bold. NA: not assessable due to absence of mutation carriers with events. Genes on the BRIDGES panel (Dorling et al., NEJM 2021) other than *ATM*, *BARD1*, *BRCA1*, *BRCA2*, *CHEK2*, *PALB2*, *RAD51C*, *RAD51D*, and *TP53* are presented here. [a] Adjusted analyses were performed by including age at diagnosis, nodal status, size category, grade, ERB-B2 receptor tyrosine kinase 2 (*ERBB2*) status of the first breast cancer, (neo)adjuvant chemotherapy, endocrine therapy and trastuzumab as covariates in the Cox regression model.

Table S36. **Association of rare missense variants in 25 putative breast cancer genes with breast cancer-specific survival.**

Gene	Unadjusted analyses		Adjusted analyses[a]		No. of women		No. of BC deaths	
	HR (95%CI)	P	HR (95%CI)	P	Non-carriers	Carriers	Non-carriers	Carriers
ABRAXAS1	0.74 (0.42-1.30)	3.0E-01	0.78 (0.44-1.37)	3.9E-01	34235	154	3437	11
AKT1	1.40 (0.80-2.43)	2.4E-01	1.57 (0.88-2.79)	1.2E-01	34298	100	3435	14
BABAM2	0.85 (0.47-1.57)	6.1E-01	0.87 (0.47-1.60)	6.5E-01	34277	117	3436	10
BRIP1	1.03 (0.79-1.34)	8.4E-01	1.05 (0.81-1.38)	7.0E-01	33796	545	3381	57
CDH1	0.98 (0.72-1.34)	9.0E-01	1.03 (0.74-1.41)	8.8E-01	33992	403	3410	39
EPCAM	1.03 (0.63-1.68)	9.1E-01	1.05 (0.64-1.72)	8.6E-01	34237	156	3433	16
FANCC	0.97 (0.72-1.31)	8.6E-01	0.99 (0.73-1.34)	9.6E-01	33919	423	3401	43
FANCM	0.84 (0.68-1.04)	1.1E-01	0.82 (0.66-1.01)	6.3E-02	33126	1013	3328	85
GEN1	0.78 (0.57-1.08)	1.3E-01	0.78 (0.56-1.07)	1.3E-01	33936	443	3408	35
MEN1	1.45 (0.77-2.71)	2.5E-01	1.53 (0.81-2.89)	1.9E-01	34312	86	3438	11
MLH1	0.99 (0.75-1.32)	9.6E-01	0.98 (0.74-1.31)	9.1E-01	33902	496	3401	48
MRE11A	0.98 (0.70-1.35)	8.8E-01	0.96 (0.70-1.34)	8.3E-01	33976	390	3409	36
MSH2	1.07 (0.83-1.38)	6.2E-01	1.06 (0.82-1.37)	6.8E-01	33841	549	3385	61
MSH6	1.23 (0.99-1.52)	6.7E-02	1.22 (0.98-1.51)	8.0E-02	33650	723	3359	89
MUTYH	1.21 (0.89-1.64)	2.2E-01	1.17 (0.86-1.58)	3.2E-01	33979	393	3403	45
NBN	0.95 (0.69-1.29)	7.2E-01	0.89 (0.66-1.22)	4.8E-01	33902	416	3400	40
NF1	0.90 (0.68-1.19)	4.7E-01	0.92 (0.70-1.22)	5.8E-01	33829	552	3398	49
PIK3CA	0.79 (0.44-1.44)	4.4E-01	0.86 (0.47-1.58)	6.3E-01	34263	132	3439	10
PMS2	1.14 (0.90-1.44)	2.7E-01	1.13 (0.90-1.43)	2.9E-01	33758	616	3369	76
PTEN	1.35 (0.65-2.80)	4.2E-01	1.42 (0.68-3.00)	3.5E-01	34325	61	3441	8
RAD50	0.84 (0.66-1.06)	1.5E-01	0.88 (0.69-1.13)	3.2E-01	33583	722	3377	63
RECQL	0.89 (0.65-1.23)	4.8E-01	0.95 (0.68-1.32)	7.6E-01	33971	387	3408	36
RINT1	0.96 (0.72-1.27)	7.7E-01	0.96 (0.72-1.27)	7.7E-01	33864	512	3398	49
STK11	0.93 (0.42-2.06)	8.7E-01	1.22 (0.53-2.80)	6.4E-01	34340	59	3443	6
XRCC2	0.99 (0.58-1.67)	9.6E-01	1.13 (0.66-1.93)	6.6E-01	34248	143	3434	14

Abbreviations: No. = number; BC = breast cancer; HR = hazard ratio; CI = confidence interval; P = p-value.

Analyses included women from 34 studies listed in Table S1. Women who developed a CBC before study entry are excluded. The analysis for each gene excluded carriers of protein-truncating variants in that gene.

Genes on the BRIDGES panel (Dorling et al., NEJM 2021) other than *ATM*, *BARD1*, *BRCA1*, *BRCA2*, *CHEK2*, *PALB2*, *RAD51C*, *RAD51D*, and *TP53* are presented here.

[a] Adjusted analyses were performed by including age at diagnosis, nodal status, size category, grade, estrogen receptor (ER) status, ERB-B2 receptor tyrosine kinase 2 (*ERBB2*) status of the first breast cancer, (neo)adjuvant chemotherapy, endocrine therapy and trastuzumab as covariates in the Cox regression model.

Table S37. **Association of rare missense variants in 25 putative breast cancer genes with breast cancer-specific survival in women diagnosed with ER-positive first breast cancer.**

Gene	Unadjusted analyses		Adjusted analyses[a]		No. of women		No. of BC deaths	
	HR (95%CI)	P	HR (95%CI)	P	Non-carriers	Carriers	Non-carriers	Carriers
ABRAXAS1	0.72 (0.36-1.46)	3.6E-01	0.76 (0.38-1.56)	4.6E-01	22471	113	1990	7
AKT1	1.28 (0.56-2.96)	5.6E-01	1.41 (0.60-3.35)	4.3E-01	22533	54	1991	6
BABAM2	0.27 (0.09-0.82)	2.0E-02	0.28 (0.09-0.83)	2.3E-02	22508	77	1992	2
BRIP1	0.98 (0.69-1.40)	9.3E-01	1.03 (0.72-1.47)	8.8E-01	22213	346	1960	31
CDH1	0.83 (0.55-1.26)	3.8E-01	0.88 (0.58-1.35)	5.7E-01	22300	286	1976	21
EPCAM	1.42 (0.76-2.65)	2.8E-01	1.37 (0.73-2.57)	3.2E-01	22493	91	1986	11
FANCC	0.91 (0.61-1.37)	6.6E-01	0.93 (0.61-1.39)	7.1E-01	22271	286	1973	23
FANCM	0.75 (0.57-1.00)	5.0E-02	0.75 (0.56-1.00)	4.8E-02	21773	659	1932	44
GEN1	0.71 (0.45-1.11)	1.3E-01	0.69 (0.44-1.09)	1.1E-01	22290	287	1978	17
MEN1	1.88 (0.87-4.04)	1.1E-01	1.83 (0.85-3.96)	1.2E-01	22530	57	1989	8
MLH1	0.95 (0.65-1.39)	7.8E-01	0.94 (0.64-1.38)	7.5E-01	22290	298	1971	26
MRE11A	0.78 (0.49-1.23)	2.8E-01	0.77 (0.48-1.21)	2.6E-01	22317	250	1977	17
MSH2	1.15 (0.83-1.59)	3.9E-01	1.10 (0.79-1.51)	5.8E-01	22210	375	1957	39
MSH6	1.25 (0.94-1.67)	1.3E-01	1.27 (0.95-1.69)	1.1E-01	22107	465	1945	51
MUTYH	1.51 (1.03-2.21)	3.3E-02	1.40 (0.96-2.03)	8.1E-02	22325	244	1966	31
NBN	1.01 (0.67-1.53)	9.5E-01	0.97 (0.64-1.47)	8.8E-01	22273	255	1969	23
NF1	0.78 (0.54-1.13)	1.9E-01	0.77 (0.53-1.11)	1.6E-01	22200	378	1970	26
PIK3CA	0.70 (0.33-1.49)	3.5E-01	0.73 (0.34-1.55)	4.1E-01	22492	94	1991	6
PMS2	1.26 (0.94-1.69)	1.2E-01	1.24 (0.93-1.67)	1.5E-01	22173	398	1948	49
PTEN	1.53 (0.65-3.61)	3.3E-01	1.48 (0.63-3.50)	3.7E-01	22539	44	1991	6
RAD50	0.78 (0.57-1.07)	1.3E-01	0.76 (0.55-1.04)	9.0E-02	22051	480	1956	36
RECQL	1.06 (0.70-1.59)	7.9E-01	1.19 (0.78-1.80)	4.1E-01	22301	259	1970	24
RINT1	0.75 (0.50-1.12)	1.6E-01	0.79 (0.53-1.18)	2.5E-01	22236	336	1973	22
STK11	0.48 (0.14-1.63)	2.4E-01	0.72 (0.19-2.67)	6.2E-01	22548	41	1995	2
XRCC2	0.69 (0.33-1.47)	3.4E-01	0.78 (0.36-1.69)	5.3E-01	22487	98	1991	6

Abbreviations: No. = number; BC = breast cancer; HR = hazard ratio; CI = confidence interval; P = p-value.

Analyses included from 34 studies listed in Table S1. Women who developed a CBC before study entry are excluded. The analysis for each gene excluded carriers of protein-truncating variants in that gene.

Genes on the BRIDGES panel (Dorling et al., NEJM 2021) other than *ATM*, *BARD1*, *BRCA1*, *BRCA2*, *CHEK2*, *PALB2*, *RAD51C*, *RAD51D*, and *TP53* are presented here.

[a] Adjusted analyses were performed by including age at diagnosis, nodal status, size category, grade, ERB-B2 receptor tyrosine kinase 2 (*ERBB2*) status of the first breast cancer, (neo)adjuvant chemotherapy, endocrine therapy and trastuzumab as covariates in the Cox regression model.

Table S38. Association of rare missense variants in 25 putative breast cancer genes with breast cancer-specific survival in women diagnosed with ER-negative first breast cancer.

Gene	Unadjusted analyses		Adjusted analyses[a]		No. of women		No. of BC deaths	
	HR (95%CI)	P	HR (95%CI)	P	Non-carriers	Carriers	Non-carriers	Carriers
ABRAXAS1	0.76 (0.20-2.87)	6.9E-01	0.75 (0.20-2.85)	6.8E-01	5644	19	832	2
AKT1	1.73 (0.72-4.16)	2.2E-01	2.23 (0.89-5.55)	8.6E-02	5644	21	828	6
BABAM2	1.34 (0.48-3.75)	5.8E-01	1.32 (0.47-3.73)	6.0E-01	5644	21	830	4
BRIP1	1.10 (0.64-1.88)	7.4E-01	1.17 (0.67-2.02)	5.8E-01	5551	102	816	14
CDH1	1.27 (0.64-2.53)	4.9E-01	1.11 (0.56-2.18)	7.7E-01	5614	49	825	9
EPCAM	0.68 (0.23-1.96)	4.7E-01	0.76 (0.25-2.25)	6.1E-01	5635	29	831	3
FANCC	1.38 (0.83-2.29)	2.2E-01	1.37 (0.82-2.28)	2.3E-01	5577	71	814	17
FANCM	1.12 (0.76-1.64)	5.8E-01	1.00 (0.68-1.46)	9.9E-01	5437	172	799	28
GEN1	1.13 (0.63-2.03)	6.7E-01	1.17 (0.65-2.10)	6.1E-01	5589	71	818	12
MEN1	1.11 (0.27-4.57)	8.8E-01	1.40 (0.32-6.21)	6.6E-01	5651	14	832	2
MLH1	0.98 (0.56-1.74)	9.6E-01	0.87 (0.49-1.53)	6.3E-01	5568	96	822	12
MRE11A	1.22 (0.64-2.34)	5.4E-01	1.23 (0.64-2.38)	5.3E-01	5594	63	823	10
MSH2	0.72 (0.38-1.34)	2.9E-01	0.74 (0.39-1.39)	3.5E-01	5584	78	824	9
MSH6	1.31 (0.84-2.03)	2.4E-01	1.24 (0.80-1.93)	3.4E-01	5541	115	812	22
MUTYH	1.00 (0.54-1.88)	9.9E-01	1.06 (0.56-2.01)	8.6E-01	5584	75	823	10
NBN	0.68 (0.35-1.32)	2.6E-01	0.67 (0.35-1.31)	2.4E-01	5577	73	823	8
NF1	1.28 (0.75-2.19)	3.6E-01	1.41 (0.82-2.44)	2.2E-01	5575	86	819	15
PIK3CA	0.74 (0.20-2.77)	6.5E-01	0.76 (0.20-2.90)	6.9E-01	5643	22	832	2
PMS2	1.08 (0.67-1.77)	7.4E-01	1.13 (0.69-1.85)	6.3E-01	5552	110	816	17
PTEN	0.89 (0.13-6.11)	9.0E-01	0.97 (0.13-6.96)	9.7E-01	5655	8	833	1
RAD50	0.81 (0.44-1.48)	4.9E-01	0.96 (0.51-1.79)	8.9E-01	5554	93	823	10
RECQL	0.64 (0.32-1.28)	2.1E-01	0.67 (0.33-1.36)	2.7E-01	5593	65	825	7
RINT1	1.33 (0.84-2.12)	2.3E-01	1.32 (0.83-2.12)	2.4E-01	5560	103	814	20
STK11	2.16 (0.45-10.37)	3.4E-01	2.11 (0.44-10.20)	3.5E-01	5658	7	832	2
XRCC2	2.12 (0.92-4.90)	7.8E-02	2.34 (1 - 5.49)	5.1E-02	5638	23	826	7

Abbreviations: No. = number; BC = breast cancer; HR = hazard ratio; CI = confidence interval; P = p-value.

Analyses included women from 34 studies listed in Table S1. Women who developed a CBC before study entry are excluded. The analysis for each gene excluded carriers of protein-truncating variants in that gene.

Genes on the BRIDGES panel (Dorling et al., NEJM 2021) other than *ATM*, *BARD1*, *BRCA1*, *BRCA2*, *CHEK2*, *PALB2*, *RAD51C*, *RAD51D*, and *TP53* are presented here.

[a] Adjusted analyses were performed by including age at diagnosis, nodal status, size category, grade, ERB-B2 receptor tyrosine kinase 2 (*ERBB2*) status of the first breast cancer, (neo)adjuvant chemotherapy, endocrine therapy and trastuzumab as covariates in the Cox regression model.

Table S39. **Sensitivity analysis for the association of protein-truncating variants in 9 breast cancer genes and of pathogenic/likely pathogenic rare missense variants in *BRCA1*, *BRCA2* and *TP53* with breast cancer-specific survival , censoring for contralateral breast cancer.**

Gene	Unadjusted analyses		Adjusted analyses[a]		No. of women		No. of BC deaths	
PTVs (unless indicated otherwise)	**HR (95%CI)**	**P**	**HR (95%CI)**	**P**	**Non-carriers**	**Carriers**	**Non-carriers**	**Carriers**
ATM	1.24 (0.84-1.84)	2.8E-01	1.07 (0.73-1.58)	7.3E-01	34151	250	3303	27
BARD1	1.16 (0.47-2.86)	7.4E-01	0.92 (0.39-2.21)	8.6E-01	34347	54	3325	5
BRCA1[b]	1.29 (0.94-1.77)	1.2E-01	0.95 (0.70-1.30)	7.5E-01	34037	364	3288	42
BRCA2[b]	**1.51 (1.18-1.94)**	**1.1E-03**	1.19 (0.93-1.51)	1.7E-01	33914	487	3258	72
CHEK2	**1.41 (1.13-1.77)**	**2.4E-03**	**1.34 (1.07-1.67)**	**1.1E-02**	33702	699	3241	89
c.1100delC	**1.39 (1.08-1.78)**	**9.2E-03**	**1.35 (1.05-1.73)**	**1.8E-02**	33702	561	3241	71
Other	1.50 (0.92-2.47)	1.1E-01	1.28 (0.79-2.08)	3.2E-01	33702	138	3241	18
PALB2	**1.71 (1.18-2.47)**	**4.3E-03**	**1.45 (1.01-2.08)**	**4.4E-02**	34177	224	3296	34
RAD51C	0.55 (0.16-1.93)	3.5E-01	0.57 (0.16-2.01)	3.8E-01	34361	40	3328	2
RAD51D	1.27 (0.51-3.16)	6.1E-01	0.81 (0.35-1.89)	6.2E-01	34370	31	3325	5
TP53[b]	**2.80 (1.24-6.30)**	**1.3E-02**	**2.32 (1.04-5.16)**	**4.0E-02**	34354	47	3322	8

Abbreviations: No. = number; BC = breast cancer; PTVs = protein-truncating variants; HR = hazard ratio; CI = confidence interval; P = p-value.

Analyses included women from 34 studies listed in Table S1. Statistically significant associations (P<5E-02) are highlighted in bold.

[a]Adjusted analyses were performed by including age at diagnosis, nodal status, size category, grade, estrogen receptor (ER) status, ERB-B2 receptor tyrosine kinase 2 (*ERBB2*) status of the first breast cancer, (neo)adjuvant chemotherapy, endocrine therapy and trastuzumab as covariates in the Cox regression model.

[b] Combined PTVs and rare pathogenic/likely pathogenic missense variants as defined in Dorling et al. (NEJM 2021).

Table S40. **Sensitivity analysis for the association of rare missense variants in 9 breast cancer genes with breast cancer-specific survival, censoring for contralateral breast cancer.**

Gene	Unadjusted analyses		Adjusted analyses[a]		No. of women		No. of BC deaths	
	HR (95%CI)	P	HR (95%CI)	P	Non-carriers	Carriers	Non-carriers	Carriers
ATM	0.99 (0.85-1.16)	8.9E-01	0.97 (0.83-1.14)	7.3E-01	32411	1740	3138	165
BARD1	1.19 (0.88-1.62)	2.6E-01	1.15 (0.85-1.57)	3.6E-01	33944	403	3281	44
BRCA1	1.12 (0.91-1.37)	2.9E-01	1.11 (0.90-1.36)	3.4E-01	33160	921	3195	97
BRCA2	1.01 (0.87-1.17)	9.2E-01	0.98 (0.84-1.14)	7.7E-01	32116	1833	3087	176
CHEK2	**1.29 (1.00-1.64)**	**4.6E-02**	1.24 (0.97-1.59)	9.1E-02	33091	611	3171	70
PALB2	1.10 (0.82-1.47)	5.3E-01	1.07 (0.80-1.43)	6.6E-01	33735	442	3249	47
RAD51C	1.20 (0.71-2.02)	5.0E-01	1.21 (0.72-2.05)	4.7E-01	34223	138	3313	15
RAD51D	0.82 (0.44-1.55)	5.4E-01	0.76 (0.41-1.42)	3.9E-01	34256	114	3316	9
TP53	**1.94 (1.32-2.86)**	**7.5E-04**	**1.70 (1.16-2.49)**	**6.6E-03**	34218	179	3297	32

Abbreviations: No. = number; BC = breast cancer; HR = hazard ratio; CI = confidence interval; P = p-value.
Analyses included women from 34 studies listed in Table S1. The analysis for each gene excluded carriers of protein-truncating variants in that gene. Statistically significant associations (P<5E-02) are highlighted in bold.
[a] Adjusted analyses were performed by including age at diagnosis, nodal status, size category, grade, estrogen receptor (ER) status, ERB-B2 receptor tyrosine kinase 2 (*ERBB2*) status of the first breast cancer, (neo)adjuvant chemotherapy, endocrine therapy and trastuzumab as covariates in the Cox regression model.

Table S41. Association of protein-truncating variants in 9 breast cancer genes and of pathogenic/likely pathogenic rare missense variants in *BRCA1*, *BRCA2* and *TP53* with overall survival.

Gene	Unadjusted analyses		Adjusted analyses[a]		No. of women		No. of deaths	
PTVs (unless indicated otherwise)	**HR (95%CI)**	**P**	**HR (95%CI)**	**P**	**Non-carriers**	**Carriers**	**Non-carriers**	**Carriers**
ATM	1.25 (0.95-1.64)	1.1E-01	1.18 (0.90-1.56)	2.3E-01	34151	250	6842	56
BARD1	1.45 (0.83-2.53)	1.9E-01	1.30 (0.75-2.25)	3.6E-01	34347	54	6884	14
BRCA1[b]	1.08 (0.87-1.34)	4.7E-01	1.20 (0.96-1.50)	1.1E-01	34037	364	6810	88
BRCA2[b]	**1.28 (1.07-1.54)**	**7.5E-03**	**1.27 (1.06-1.52)**	**1.1E-02**	33914	487	6769	129
CHEK2	**1.22 (1.04-1.43)**	**1.5E-02**	**1.21 (1.03-1.43)**	**2.0E-02**	33702	699	6735	163
c.1100delC	1.15 (0.96-1.38)	1.4E-01	1.16 (0.96-1.39)	1.2E-01	33702	561	6735	123
Other	**1.51 (1.08-2.10)**	**1.5E-02**	**1.43 (1.02-1.99)**	**3.6E-02**	33702	138	6735	40
PALB2	1.29 (0.98-1.69)	7.1E-02	1.18 (0.90-1.55)	2.2E-01	34177	224	6842	56
RAD51C	1.11 (0.55-2.26)	7.7E-01	0.98 (0.49-1.95)	9.5E-01	34361	40	6890	8
RAD51D	1.34 (0.67-2.66)	4.0E-01	1.08 (0.55-2.09)	8.3E-01	34370	31	6889	9
TP53[b]	**3.10 (1.79-5.36)**	**5.4E-05**	**3.47 (1.98-6.09)**	**1.5E-05**	34354	47	6880	18

Abbreviations: No. = number; PTVs = protein-truncating variants; HR = hazard ratio; CI = confidence interval; P = p-value. Analyses included women from 34 studies listed in Table S1. Women who developed a CBC before study entry are excluded. Statistically significant associations (P<5E-02) are highlighted in bold.

[a] Adjusted analyses were performed by including age at diagnosis, nodal status, size category, grade, estrogen receptor (ER) status, ERB-B2 receptor tyrosine kinase 2 (*ERBB2*) status of the first breast cancer, (neo)adjuvant chemotherapy, endocrine therapy and trastuzumab as covariates in the Cox regression model.

[b] Combined PTVs and rare pathogenic/likely pathogenic missense variants as defined in Dorling et al. (NEJM 2021).

Table S42. Association of rare missense variants in 9 breast cancer genes with overall survival.

Gene	Unadjusted analyses		Adjusted analyses[a]		No. of women		No. of deaths	
	HR (95%CI)	P	HR (95%CI)	P	Non-carriers	Carriers	Non-carriers	Carriers
ATM	0.99 (0.88-1.10)	8.0E-01	1.00 (0.90-1.12)	9.8E-01	32411	1740	6498	344
BARD1	1.04 (0.83-1.31)	7.2E-01	1.02 (0.81-1.28)	8.4E-01	33944	403	6806	78
BRCA1	1.04 (0.90-1.21)	5.9E-01	1.10 (0.94-1.27)	2.3E-01	33160	921	6633	185
BRCA2	1.02 (0.92-1.13)	6.9E-01	1.02 (0.92-1.14)	6.8E-01	32116	1833	6405	374
CHEK2	1.14 (0.96-1.37)	1.4E-01	**1.21 (1.01-1.46)**	**4.0E-02**	33091	611	6609	126
PALB2	1.10 (0.90-1.35)	3.6E-01	1.06 (0.86-1.30)	6.0E-01	33735	442	6748	94
RAD51C	0.94 (0.63-1.39)	7.5E-01	0.93 (0.63-1.39)	7.3E-01	34223	138	6866	24
RAD51D	0.65 (0.40-1.03)	6.9E-02	**0.60 (0.38-0.96)**	**3.2E-02**	34256	114	6874	15
TP53	**1.45 (1.06-1.97)**	**1.9E-02**	**1.47 (1.08-2.00)**	**1.5E-02**	34218	179	6849	46

Abbreviations: No. = number; HR = hazard ratio; CI = confidence interval; P = p-value.

Analyses included women from 34 studies listed in Table S1. Women who developed a CBC before study entry are excluded. The analysis for each gene excluded carriers of protein-truncating variants in that gene. Statistically significant associations (P<5E-02) are highlighted in bold.

[a] Adjusted analyses were performed by including age at diagnosis, nodal status, size category, grade, estrogen receptor (ER) status, ERB-B2 receptor tyrosine kinase 2 (*ERBB2*) status of the first breast cancer, (neo)adjuvant chemotherapy, endocrine therapy and trastuzumab as covariates in the Cox regression model.

Supplementary methods

Rare missense variants calling and analyses

Rare missense variants (MSVs) identified in the BRIDGES study[1] were analyzed in aggregate, by gene. For *BRCA1*, *BRCA2* and *TP53*, subsets of rare MSVs were also considered, which were likely to be considered pathogenic according to commonly accepted guidelines as described previously[1]. More specifically, for *BRCA1* and *BRCA2*, MSVs were classified as pathogenic or likely pathogenic by either ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/) or the ENIGMA *BRCA1/2* expert panel guidelines (https://enigmaconsortium.org/). For *TP53*, additional definitions of (likely) pathogenic, based on *TP53* Variant Curation Expert Panel Specifications[2] of the American College of Medical Genetics (ACMG) guidelines[3], and on a published quantitative model for *TP53* missense variant[4] were also used.

Definition of contralateral breast cancer and survival

Primary second tumors were defined by individual studies. In particular, data on laterality was collected by individual studies and reported to the central Breast Cancer Association Consortium (BCAC) database. Information about follow-up, including vital status was also collected by individual studies. Table S1 provides, for each included study, information on: 1) how follow-up (including vital status) information was obtained; 2) how disease recurrence/progression was obtained; 3) how information on contralateral breast cancer was obtained and how it was defined; and 4) when the most recent attempt to have

complete follow-up was. Sources of data varied across studies but mostly came from medical records. A variable in the central BCAC database indicates, for women who died, whether death was due to breast cancer, to other causes, or whether it was unknown, at least in the study database.

Multiple imputation of missing data

Multiple imputation was performed to address the presence of missing data in several clinical and pathological variables included as covariates in the multivariable Cox regression models. The R package MICE (version 3.13.0) was used to impute 10 datasets through 30 iterations of the multivariate imputation by chained equations (MICE) algorithm. Imputation was performed on a total of 35232 women with available vital status and number of years from diagnosis of the first breast cancer to last follow-up (Table S4).

The list of imputed variables, corresponding percentage of missing values, imputation methods, and information about pre-processing of the data can be found in Table S5. Variables included in the imputation process were imputed according to the number of missing values, from the least to the most missing.

For each imputed variable, predictors in the corresponding imputation model were selected among all the variables included in the imputation process based on the correlation coefficient with the variable to impute (≥0.125) and the proportion of observed values among the cases with missing data on the variable to impute (≥0.200). In particular, neo-adjuvant chemotherapy status (yes vs no) was added as predictor in the imputation models of neoadjuvant anthracyclines status, neoadjuvant taxanes status and neoadjuvant CMF-like chemotherapy status. Year of diagnosis was included as predictor in the imputation models of (neo)adjuvant chemotherapy status (yes vs no), adjuvant

endocrine therapy status (yes vs no), and adjuvant trastuzumab status (yes vs no). The variable “study” was included in all imputation models, in order to preserve the heterogeneity among studies as much as possible, and because in case of systematic missing values (variables not measured/reported by entire studies) it is an informative predictor, which needs to be included to fulfill the missing at random assumption[5].

The Nelson-Aalen estimator of the baseline cumulative hazard and the event indicator of breast cancer-specific survival and overall survival were included in all imputation models to improve imputation, as well as the time to contralateral breast cancer (CBC) and the corresponding event indicator [6]. Due to the presence of missing values, time to CBC and corresponding event indicator were also imputed, but the imputed values for these two variables were not used in the adjusted CBC risk analyses, which were based only on women with observed CBC status and time to CBC recorded.

Estimates from the analyses across different imputed datasets were combined via Rubin’s rule [7,8].

Heterogeneity of hazard ratio (HR) estimates for ER-positive and ER-negative first breast cancer

Heterogeneity of the HR estimates for the carrier status by ER status of the first BC was tested in both unadjusted analyses and analyses adjusted for first BC tumor characteristics (size, grade, lymph node status, ERB-B2 receptor tyrosine kinase 2 (ERBB2, MIM: 164870) status), age at diagnosis and systemic treatment (endocrine therapy, (neo)adjuvant chemotherapy and trastuzumab). For HR estimates from the unadjusted analyses, the heterogeneity test was performed by comparing a model

including the main effects and an interaction term between carrier status and the ER status of the first BC (full model), with a model without the interaction term (reduced model), using a likelihood ratio test via the “anova” function in R. For HR estimates from the adjusted analyses, the full and reduced model compared additionally included size, grade, lymph node status, age at diagnosis of the first BC, endocrine therapy, (neo)adjuvant chemotherapy and trastuzumab as covariates and were compared via the D1-statistic (multivariate Wald test) across multiply imputed datasets [9], using the R package MICE (version 3.13.0).

CBC risk analyses by age at first BC diagnosis for *BRCA1*, *BRCA2*, *TP53*

Unadjusted CBC analyses were performed separately for combined PTVs and pathogenic/likely pathogenic MSVs in *BRCA1*, *BRCA2*, and in *TP53,* within subgroups of women diagnosed with first BC at age younger than 40 years and at age equal or older than 40 years. Heterogeneity of the HR estimates for the carrier status by age at diagnosis of the first BC was tested by comparing a model including the main effects and an interaction term between carrier status and a binary variable for age at first BC diagnosis with categories “< 40 years” and “≥ 40 years” (full model), with a model without the interaction term (reduced model), using a likelihood ratio test via the “anova” function in R.

CBC cumulative incidence estimation

CBC cumulative incidence estimates for carriers and non-carriers of PTVs in *ATM*, *BARD1*, *CHEK2*, *PALB2*, *RAD51C*, and *RAD51D,* and pathogenic/likely pathogenic MSVs in *BRCA1*, *BRCA2* and *TP53*, accounting for death from any cause as competing event, were computed using the R package "survival"[10,11] as explained in the vignette "Multi-state models and competing risks" available at https://CRAN.R-project.org/package=survival.

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