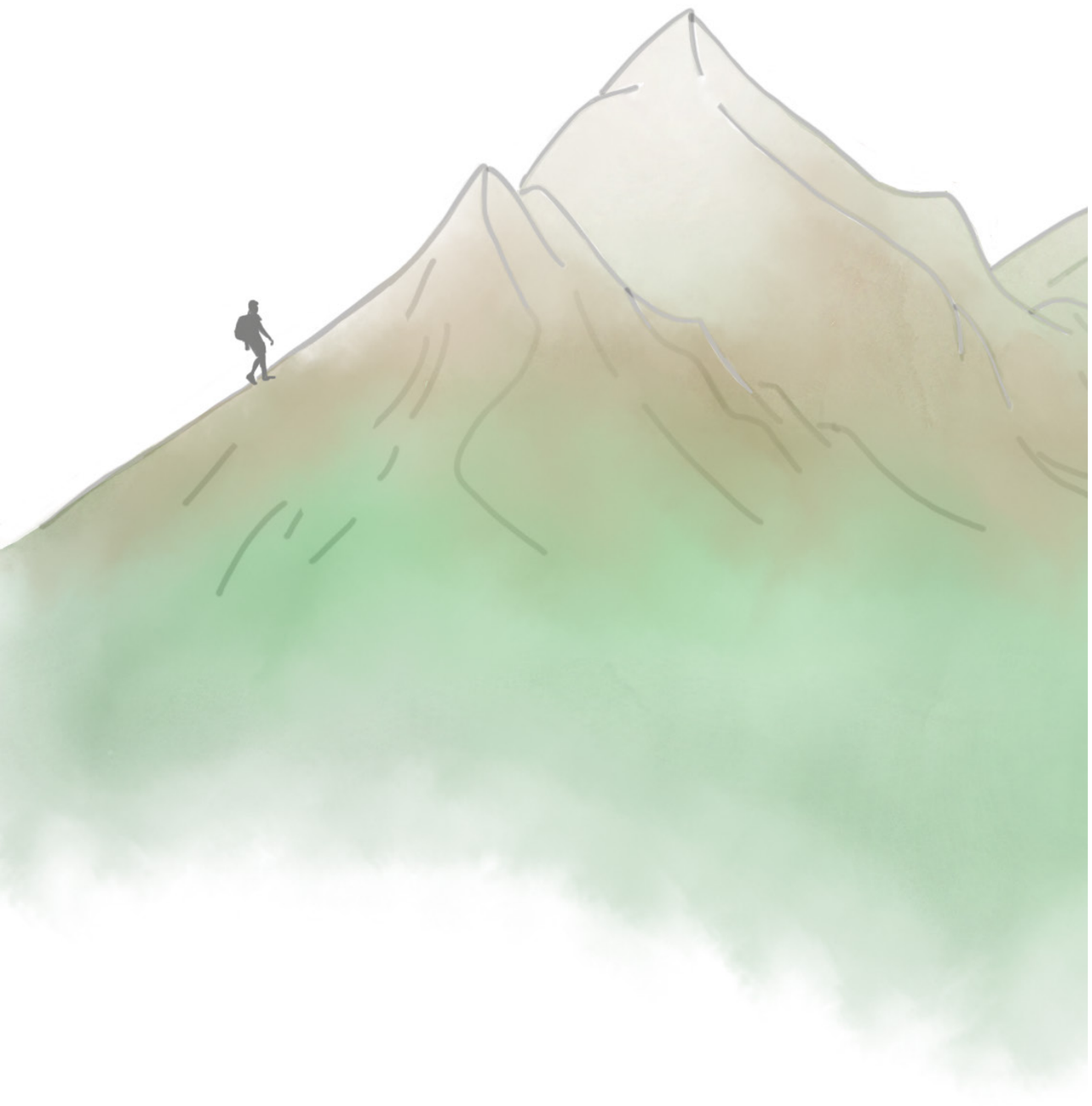
Prediction of contralateral breast cancer: statistical aspects and prediction performance

Giardiello, D.



Chapter 2

Prediction and clinical utility of a contralateral breast cancer risk model

Breast Cancer Research. 2019 Dec; 21(1):1-3[#]
https://breast-cancer-research.biomedcentral.com/articles/10.1186/s13058-019-1221-1

Daniele Giardiello
Ewout W. Steyerberg,
Michael Hauptmann,
Muriel A. Adank, Delal Akdeniz, Carl Blomqvist, Stig E. Bojesen, Manjeet K. Bolla, Mariël Brinkhuis, Jenny Chang-Claude, Kamila Czene, Peter Devilee, Alison M. Dunning, Douglas F. Easton, Diana M. Eccles, Peter A. Fasching, Jonine Figueroa, Henrik Flyger, Montserrat García-Closas, Lothar Haeberle, Christopher A. Haiman, Per Hal, Ute Hamann, John L. Hopper, Agnes Jager, Anna Jakubowska, Audrey Jung, Renske Keeman, Iris Kramer, Diether Lambrechts, Loic Le Marchand, Annika Lindblom, Jan Lubiński, Mehdi Manoochehri, Luigi Mariani, Heli Nevanlinna, Hester S.A. Oldenburg, Saskia Pelders, Paul D.P. Pharoah, Mitul Shah, Sabine Siesling, Vincent T.H.B.M. Smit, Melissa C. Southey, William J. Tapper, Rob A.E.M. Tollenaar, Alexandra J. van den Broek, Carolien H.M. van Deurzen, Flora E. van Leeuwen, Chantal van Ongeval, Laura J. Van't Veer, Qin Wang, Camilla Wendt, Pieter J. Westenend,
Maartje J. Hooning
Marjanka K. Schmidt

[#]Author affiliations available on the journal's website

ABSTRACT

Background

Breast cancer survivors are at risk for contralateral breast cancer (CBC), with the consequent burden of further treatment and potentially less favorable prognosis. We aimed to develop and validate a CBC risk prediction model, and evaluate its applicability for clinical decision-making.

Methods

We included data of 132,756 invasive non-metastatic breast cancer patients from 20 studies with 4,682 CBC events and a median follow-up of 8.8 years. We developed a multivariable Fine and Gray prediction model (PredictCBC-1A) including patient, primary tumor, and treatment characteristics, and *BRCA1/2* germline mutation status, accounting for the competing risks of death and distant metastasis. We also developed a model without *BRCA1/2* mutation status (PredictCBC-1B) since this information was available for only 6% of patients and is routinely unavailable in the general breast cancer population. Prediction performance was evaluated using calibration and discrimination, calculated by a time-dependent Area-Under-the-Curve (AUC) at 5 and 10 years after diagnosis of primary breast cancer, and an internal-external cross-validation procedure. Decision curve analysis was performed to evaluate the net benefit of the model to quantify clinical utility.

Results

In the multivariable model, *BRCA1/2* germline mutation status, family history and systemic adjuvant treatment showed the strongest associations with CBC risk. The AUC of PredictCBC-1A was 0.63 (95% prediction interval (PI) at 5 years: 0.52–0.74; at 10 years: 0.53–0.72). Calibration in-the-large was -0.13 (95%PI: -1.62–1.37) and the calibration slope was 0.90 (95%PI: 0.73–1.08). The AUC of Predict-1B at 10 years was 0.59 (95% PI: 0.52–0.66); calibration was slightly lower. Decision curve analysis for preventive contralateral mastectomy showed potential clinical utility of PredictCBC-1A between thresholds of 4-10% 10-year CBC risk for *BRCA1/2* mutation carriers and non-carriers.

Conclusions

We developed a reasonably calibrated model to predict the risk of CBC in women of European-descent, however, prediction accuracy was moderate. Our model shows potential for improved risk counseling, but decision making regarding contralateral preventive mastectomy, especially in the general breast cancer population where limited information of the mutation status in *BRCA1/2* is available, remains challenging.

INTRODUCTION

Breast cancer (BC) is a major burden for women's health[1]. Survival has improved substantially over the past half century due to earlier detection and advanced treatment modalities, for example in the Netherlands, 10-year survival of a first primary BC improved from 40% in 1961-1970 to 79% in 2006-2010[2]. Consequently, an increasing numbers of BC survivors are at risk to develop a new primary tumor in the opposite (contralateral) breast, with subsequent treatment and potentially less favorable prognosis[3]. BC survivors are more likely to develop contralateral breast cancer (CBC) compared to healthy women to develop a first primary BC[4].

Women at elevated CBC risk have been identified to be *BRCA1/2* and *CHEK2* c.1100del mutation carriers and to have a BC family history, particular a family history of bilateral BC[5-10]. For *BRCA1/2* mutation carriers, in whom CBC risk is high, contralateral preventive mastectomy (CPM) is often offered[11]. However, the average risk of CBC among all first BC survivors is still relatively low, with an incidence of ~0.4% per year[12-14]. Despite this, in recent years, CPM frequency has increased among women in whom CBC risk is low[15]. For these reasons, there is an urgent need for improved individualized prediction of CBC risk, both to facilitate shared-decision making of physicians and women regarding treatment and prevention strategies for those at high CBC risk and to avoid unnecessary CPM or surveillance mammography after first primary BC when CBC risk is low.

To our knowledge, only one specific CBC risk prediction model (CBCrisk) has been developed to date. CBCrisk used data on 1,921 CBC cases and 5,763 matched controls with validation in two independent US studies containing a mix of invasive and *in-situ* BC[16, 17]. Moreover, the level of prediction performance measures such as calibration and discrimination needed for a CBC risk prediction to be clinically useful have not yet been addressed[18].

Our aim was two-fold: first, to develop and validate a CBC risk prediction model using a large international series of individual patient data including 132,756 patients with a first primary invasive BC between 1990 and 2013 from multiple studies in Europe, US and Australia with 4,682 incident CBCs; and second, to evaluate the potential clinical utility of the model to support decision making.

MATERIAL AND METHODS

Study population

We used data from five main sources: three studies from the Netherlands, 16 studies from

the Breast Cancer Association Consortium (BCAC), and a cohort from the Netherlands Cancer Registry[19-22]. For details regarding data collection and patient inclusion see **Supplementary Material section: Data and patient selection** and **TableS1**, and **Table S2**. We included female patients with invasive non-metastatic first primary BC with no prior history of cancer (except for non-melanoma skin cancer). The studies were either population- or hospital-based series; most women were of European-descent. We only included women diagnosed after 1990 to have a population with diagnostic and treatment procedures likely close to modern practice and at the same time sufficient follow-up to study CBC incidence; in total 132,756 women from 20 studies were included. All studies were approved by the appropriate ethics and scientific review boards. All women provided written informed consent or did not object to secondary use of clinical data in accordance with Dutch legislation and codes of conduct[23, 24].

Available data and variable selection

Several factors have been shown or suggested to be associated with CBC risk, including age at first BC, family history for BC, *BRCA1/2* and *CHEK2* c.1100del mutations, body mass index (BMI), breast density change, (neo)adjuvant chemotherapy, endocrine therapy, CPM, and characteristics of the first BC such as histology (lobular vs ductal), estrogen receptor (ER) status, lymph node status, tumor size, and TNM stage [5, 9, 12, 25-36]. The choice of factors to include in the analyses was determined by evidence from literature, availability of data in the cohorts, and current availability in clinical practice. We extracted the following information: *BRCA1/2* germline mutation, (first degree) family history of primary BC, and regarding primary BC diagnosis: age, nodal status, size, grade, morphology, ER status, progesterone-receptor (PR), human epidermal growth factor receptor 2 (HER2) status, administration of adjuvant and/or neoadjuvant chemotherapy, adjuvant endocrine therapy, adjuvant trastuzumab therapy, radiotherapy. We excluded PR status and TNM stage of the primary BC due to collinearity with ER status and the size of the primary tumor, respectively. In the current clinical practice, only patients with ER-positive tumors receive endocrine therapy and only patients with HER2-positive tumors receive trastuzumab; these co-occurrences were considered in the model by using composite categorical variables. More information is available online about the factors included in the analyses **(Supplementary Material: Data patient selection** and **Figure S1)**, follow-up per dataset, and study design **(Table S2)**.

Statistical analyses

All analyses were performed using SAS (SAS Institute Inc., Cary, NC, USA) and R software[37].

Primary endpoint, follow-up and predictors

The primary endpoint in the analyses was *in-situ* or invasive metachronous CBC. Follow-up started three months after invasive first primary BC diagnosis, in order to exclude synchronous CBCs, and ended at date of CBC, distant metastasis (but not at loco-regional relapse), CPM, or last date of follow-up (due to death, being lost to follow-up, or end of study), whichever occurred first. The follow-up of 27,155 (20.4%) women from the BCAC studies, recruited more than 3 months after diagnosis of the first primary BC (prevalent cases) started at recruitment (left truncation). Distant metastasis and death due to any cause were considered as competing events. Patients who underwent CPM during the follow-up were censored because the CBC risk was almost zero after a CPM[38].Missing data were multiply imputed by chained equations (MICE) to avoid loss of information due to case-wise deletion[39, 40]. Details about the imputation model, strategy used, and the complete case analysis, are provided in the **Supplementary Material: Multiple Imputation of missing values, Complete case analysis,** and **Model diagnostics and baseline recalibration** and **Tables S3 and S4**

Model development and validation

For model development, we used a multivariable Fine and Gray model regression to account for death and distant metastases as competing events[41, 42]. Heterogeneity of baseline risks between studies was taken into account using the study as a stratification term. A stratified model allows the baseline subdistribution hazard to be different across the studies and parameter estimation is performed by maximization of the partial likelihood per study. A Breslow-type estimator was used to estimate the baseline cumulative subdistribution hazard per study. The assumption of proportional subdistribution hazards was graphically checked using Schoenfield residuals[43]. The resulting subdistributional hazard ratios (sHRs) and corresponding 95% confidence intervals (CI) were pooled from the 10 imputed data sets using Rubin's rules[44]. We built a nomogram for estimating the 5- and 10- year cumulative incidence of CBC as a graphical representation of the multivariable risk prediction model[45].

The validity of the model was investigated by leave-one-study-out cross-validation; i.e., in each validation step all studies are used except one in which the validity of the model is evaluated[46, 47]. Since the ABCS study and some studies from BCAC had insufficient CBC events required for reliable validation, we used the geographic area as unit of splitting. We had 20 studies in five main sources: 17 out of 20 studies that were combined in 4 geographic areas. In total, 3 studies and 4 geographic areas were used to assess the prediction performance of the model (see **Supplementary Material: Leave-one-study-out cross-validation** and **Table S5**)[47, 48].

The performance of the model was assessed by discrimination ability to differentiate between patients who experienced CBC and those who did not, and by calibration, which measures the agreement between observed and predicted CBC risk. Discrimination

was quantified by time-dependent Area under the ROC Curves (AUCs) based on Inverse Censoring Probability Weighting at 5 and 10 years [49, 50]. In presence of competing risks, the R package timeROC provides two types of AUC according to different definition of time-dependent cases and controls. AUCs were calculated considering a patient who developed a CBC as a case and a patient free of any event as a control at 5 and 10 years[50]. Values of AUCs close to 1 indicate good discriminative ability, while values close to 0.5 indicated poor discriminative ability. Calibration was assessed by the calibration-in-the-large and slope statistic[51]. Calibration-in-the-large lower or higher than zero indicates that prediction is systematically too high or low, respectively. A calibration slope of 1.0 indicates good overall calibration; slopes below (above) 1.0 indicate over (under) estimation of risk by the model.

To allow for heterogeneity among studies, a random-effect meta-analysis was performed to provide summaries of discrimination and calibration performance. The 95% prediction intervals (PI) indicated the likely range for the prediction performances of the model in a new dataset. Further details about the validation process are provided in **Supplementary Leave-one-study-out cross-validation**.

Clinical utility

The clinical utility of the prediction model was evaluated using decision curve analysis (DCA)[52, 53]. Such a decision may apply to more or less intensive screening and follow-up or to decision of a CPM. The key part of the DCA is the net benefit, which is the number of true-positive classifications (in this example: the benefit of CPM to a patient who would have developed a CBC) minus the number of false-positive classifications (in this example: the harm of unnecessary CPM in a patient who would not have developed a CBC). The false-positives are weighted by a factor related to the relative harm of a missed CBC versus an unnecessary CPM. The weighting is derived from the threshold probability to develop a CBC using a defined landmark time point (e.g. CBC risk at 5 or 10 years)[54]. For example, a threshold of 10% implies that CPM in 10 patients, of whom one would develop CBC if untreated, is acceptable (thus performing 9 unnecessary CPMs). The net benefit of a prediction model is traditionally compared with the strategies of treat all or treat none. Since the use of CPM is generally only suggested among *BRCA1/2* mutation carriers, for a more realistic illustration the decision curve analysis was reported among *BRCA1/2* mutation carriers and non-carriers[55]. See **Supplementary material: Clinical utility** for details.

RESULTS

A total of 132,756 invasive primary BC women diagnosed between 1990 and 2013, with 4,682 CBC events, from 20 studies, were used to derive the model for CBC risk (**Table S2**). Median follow-up time was 8.8 years and CBC cumulative incidences at 5 and 10 years were 2.1% and 4.1%, respectively. Details of the studies and patient, tumor, and treatment characteristics are provided in **Table S6**. The multivariable model with estimates for all included factors is shown in **Table 1**. *BRCA1/2* germline mutation status, family history and systemic adjuvant treatment showed the strongest associations with CBC risk.

Table 1. Multivariable subdistribution hazard model for contralateral breast cancer risk

Factor (category) at primary breast cancer	Multivariable analysis	
	sHR	95% CI
Age, *years*	0.68*	0.62 - 0.74*
Family history (yes versus no)	1.35	1.27 - 1.45
BRCA mutation		
BRCA1 versus non-carrier	3.68	3.34 - 4.07
BRCA2 versus non-carrier	2.56	2.36 - 2.78
Nodal status (positive versus negative)	0.87	0.80 - 0.93
Tumor size, *cm*		
(2,5] versus ≤ 2	0.95	0.89 - 1.02
> 5 versus ≤ 2	1.14	0.99 - 1.31
Morphology (lobular including mixed versus ductal including other)	1.23	1.14 - 1.34
Grade		
Moderately differentiated versus well differentiated	0.89	0.82 - 0.96
Poorly differentiated versus well differentiated	0.75	0.70 - 0.82
Chemotherapy (yes versus no)	0.77	0.70 - 0.84
Radiotherapy to the breast (yes versus no)	1.01	0.95 - 1.08
ER (positive or negative) / endocrine therapy (yes or no)		
Negative/no versus positive/yes	1.43	1.30 - 1.57
Positive/no versus positive/yes	1.75	1.61 - 1.90
HER2 (positive or negative) / trastuzumab therapy (yes or no)		
Negative/no versus positive/yes	1.08	0.93 - 1.27
Positive/no versus positive/yes	0.99	0.83 - 1.18

Abbreviations: sHR: subdistributional hazard ratio; CI: confidence interval; ER: estrogen receptor; HER2: human epidermal growth factor receptor 2; *Age was parameterized as a linear spline with one interior knot at 50 years. For representation purposes, we here provide the sHR for the 75th versus the 25th percentile. For more details about age parameterization, see also Supplementary Methods.

The prediction performance of the main model (PredictCBC, version 1A) based on the leave-one-study-out cross-validation method is shown in **Figure 1**. The AUC at 5 years was 0.63 (95% confidence interval (CI): 0.58–0.67; 95% prediction interval (PI): 0.52–0.74)); the AUC at 10 years was also 0.63 (95%CI: 0.59–0.66; 95%PI: 0.53–0.72). Calibrations showed some indications of overestimation of risk. The calibration-in-

the-large was -0.13 (95%CI: -0.66–0.40; 95%PI: -1.62–1.37). The calibration slope was 0.90 (95%CI: 0.79–1.02; 95%PI: 0.73–1.08) in the cross-validation. Calibration plots are provided in **Figure S2 and S3**.

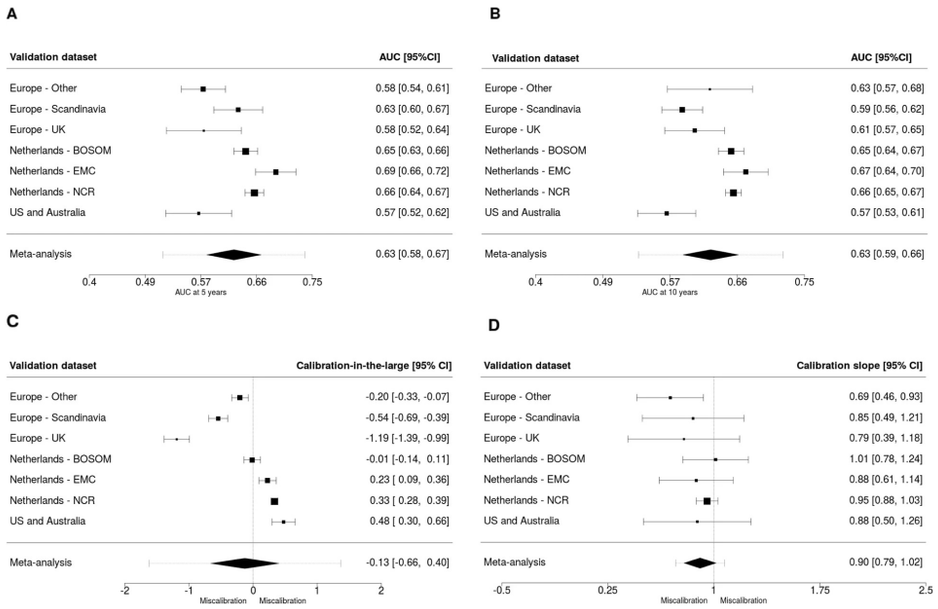


Figure 1. Analysis of predictive performance in leave-one-study-out cross-validation.
Panel A and B show the discrimination assessed by a time-dependent AUC at 5 and 10 years, respectively. Panel C shows the calibration accuracy measured with calibration in-the-large. Panel D shows the calibration accuracy measured with calibration slope. The black squares indicate the estimated accuracy of a model built using all remaining studies or geographic areas. The black horizontal lines indicate the corresponding 95% confidence intervals of the estimated accuracy (interval whiskers). The black diamonds indicate the mean with the corresponding 95% confidence intervals of the predictive accuracy and the dashed horizontal lines indicate the corresponding 95% prediction intervals.

The nomogram representing a graphical tool for estimating the CBC cumulative incidence at 5 and 10 years based on our model and the estimated baseline of the Dutch Cancer Registry is shown in **Figure 2**. In the nomogram, the categories of each factor are assigned a score using the topmost 'Points' scale, then all scores are summed up to obtain the 'Total points', which relate to the cumulative incidence of CBC. The formulae of the models (PredictCBC-1A and 1B) providing the predicted cumulative incidence are given in **Supplementary Material: Formula to estimate the CBC risk** and **Formula to estimate CBC risk in patients not tested for *BRCA***.

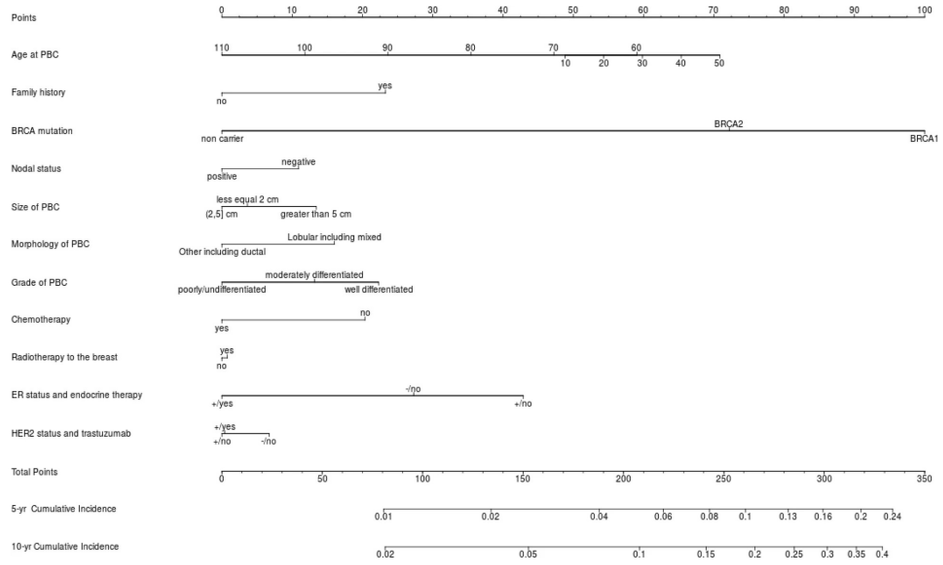


Figure 2. Nomogram for prediction of 5- and 10-year contralateral breast cancer cumulative incidence.
The 5- and 10-years contralateral breast cancer cumulative incidence is calculated by taking the sum of the risk points, according to patient, first primary breast cancer tumor, and treatment characteristics. For each factor, the number of associated risk points can be determined by drawing a vertical line straight up from the factor's corresponding value to the axis with risk points (0-100). The total points axis (0-350) is the sum of the factor's corresponding values determined by every individual patient's characteristics. Draw a line straight down from the total points axis to find the 5- and 10-years cumulative incidence.
PBC=primary breast cancer; ER=estrogen receptor status; HER2= human epidermal growth factor receptor 2; yr=year

The DCAs for preventive contralateral mastectomy showed potential clinical utility of PredictCBC-1A between thresholds of 4-10% 10-year CBC risk for *BRCA1/2* mutation carriers and non-carriers (**Table 2**). For example, if we find it acceptable that one in 10 patients for whom a CPM is recommended develops a CBC, a risk threshold of 10% may be used to define high and low risk *BRCA1/2* mutation carriers based on the absolute 10-year CBC risk prediction estimated by the model. Compared with a strategy recommending CPM to all carriers of a mutation in *BRCA1*/2, this strategy avoids 161 CPMs per 1,000 patients. In contrast, almost no non *BRCA1/2* mutation carriers reach the 10% threshold (the general BC population, **Figure 3**). The decision curves provide a comprehensive overview of the net benefit for a range of harm-benefit thresholds at 10-year CBC risk (**Figure 4**).

Decision curves for CBC risk at 5 year and the corresponding clinical utility are provided in **Figure S4** and **Table S7**, respectively.

Table 2: Clinical utility of the 10-year contralateral breast cancer risk prediction model. At the same probability threshold, the net benefit is exemplified in *BRCA1/2* mutation carriers (for avoiding unnecessary CPM) and non-carriers (performing necessary CPM).

		BRCA1/2 mutation carriers		Non-carriers	
Probability threshold p_t (%)	Unnecessary CPMs needed to prevent a CBC*	Net benefit versus treat all patients with CPM (per 1000)	Avoided unnecessary CPMs per 1000 patients	Net benefit versus treat none (per 1000)	Performed necessary CPMs per 1000 patients
4	24.0	0.0	0.0	3.9	93.6
5	19.0	0.0	0.0	2.1	39.9
6	15.7	0.1	1.6	0.5	7.8
7	13.3	1.9	25.2	0.1	1.3
8	11.5	5.5	63.3	0.0	0.0
9	10.1	10.7	108.2	0.0	0.0
10	9.0	17.9	161.1	0.0	0.0

CPM: contralateral preventive mastectomy; CBC: contralateral breast cancer;
*The number of unnecessary contralateral mastectomies needed to prevent a CBC is calculated by: $(1-p_t)/p_t$. See also Supplementary Methods.

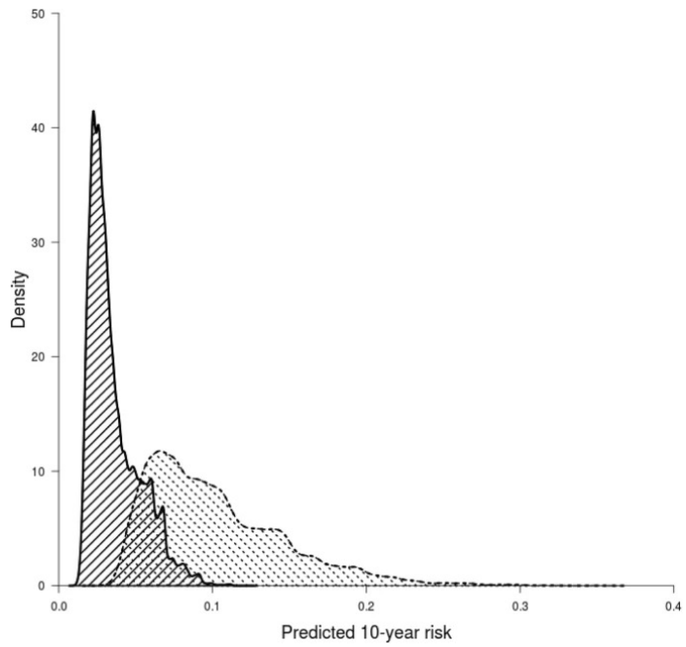
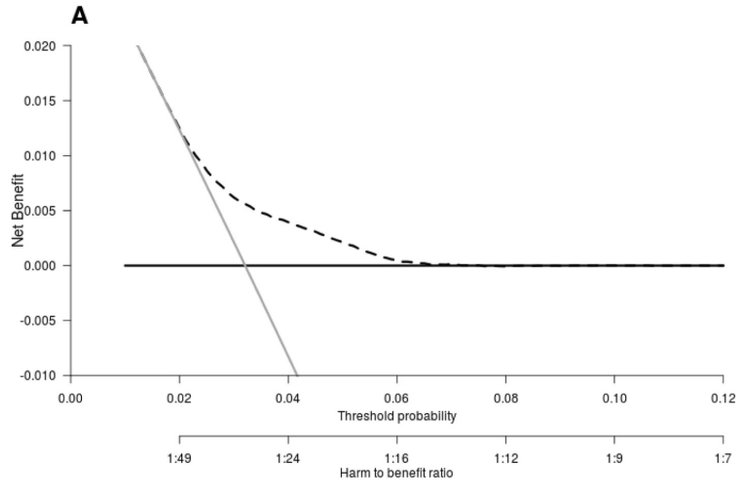


Figure 3: Density distribution of 10-year predicted contralateral breast cancer absolute risk within non-carriers (area with black solid lines) and *BRCA1/2* mutation carriers (area with black dashed lines).



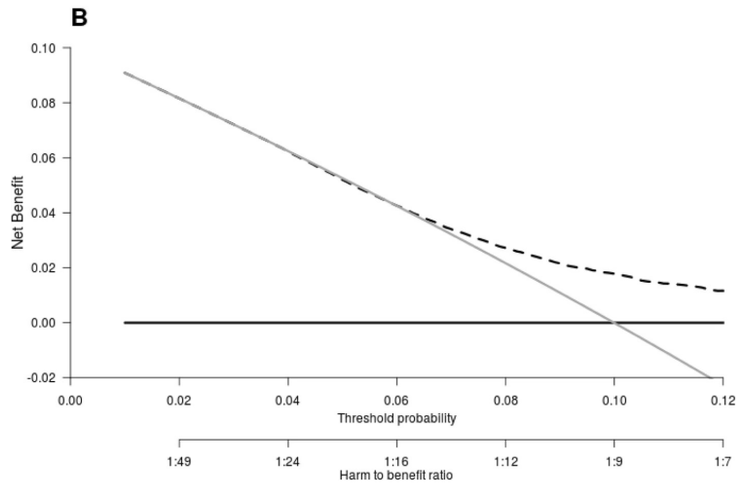


Figure 4: Decision curve analysis at 10 years for the contralateral breast cancer risk model including *BRCA* mutation information.
Panel A shows the decision curve to determine the net benefit of the estimated 10-year predicted contralateral breast cancer (CBC) cumulative incidence for patients without a *BRCA1/2* gene mutation using the prediction model (dotted black line) compared to not treating any patients with contralateral preventive mastectomy (CPM) (black solid line). Panel B shows the decision curve to determine the net benefit of the estimated 10-year predicted CBC cumulative incidence for *BRCA1/2* mutation carriers using the prediction model (dotted black line) versus treating (or at least counseling) all patients (grey solid line). The y-axis measures net benefit, which is calculated by summing the benefits (true positives, i.e., patients with a CBC who needed a CPM) and subtracting the harms (false positives, i.e., patients with CPM who do not need it). The latter are weighted by a factor related to the relative harm of a non-prevented CBC versus an unnecessary CPM. The factor is derived from the threshold probability to develop a CBC at 10 years at which a patient would opt for CPM (e.g. 10%). The x-axis represents the threshold probability. Using a threshold probability of 10% implicitly means that CPM in 10 patients of whom one would develop a CBC if untreated is acceptable (9 unnecessary CPMs, harm to benefit ratio 1:9).

We also derived a risk prediction model (PredictCBC, version 1B) omitting *BRCA* status to provide CBC risk estimates for first BC patients not tested for *BRCA1/2* mutations. This model has slightly lower prediction performance; AUC at 5 and 10 years was both 0.59 (at 5 years: 95% CI: 0.54–0.63; 95% PI: 0.46–0.71; at 10 years:0.56–0.62; 95% PI: 0.52–0.66), calibration-in-the-large was -0.17 (95% CI: -0.72–0.38; 95% PI: -1.70–1.36) and calibration slope was 0.81 (95% CI: 0.63–0.99; 95% PI: 0.50–1.12) (**Supplementary Material Results of the prediction model without *BRCA* mutation**). Details of development, validation, and clinical utility are provided in **Tables S8-10** and **Figures S5-10**.

In a sensitivity analysis (see **Supplementary Material: Assessment of limited information of CPM**), we studied the impact of CPM on our results using two studies, in which CPM information was (almost) completely available. The lack of CPM information on cumulative incidence estimation hardly affected the results of our analyses (**Figure S11**).

DISCUSSION

Using established risk factors for CBC which are currently available in clinical practice, we developed PredictCBC, which can be used to calculate 5- and 10-year absolute CBC risk. The risk prediction model includes carriership of *BRCA1/2* mutations, an important determinant of CBC risk in the decision-making process[6].

The calibration of the model was reasonable and discrimination moderate within the range of other tools commonly used for routing counseling and decision-making in clinical oncology for primary BC risk[56-59]. As expected, the prediction accuracy was lower when we omitted the *BRCA* mutation carrier status although the prevalence of *BRCA* mutations among BC patients is quite low (2-4%)[60, 61].

In the breast cancer population, CBC is a relatively uncommon event (~0.4% per year) and difficult to predict. Therefore physicians should carefully consider which patients should consider CPM using a prediction model[62]. The current clinical recommendations of CPM are essentially based on the presence of a mutation in the *BRCA1/2* genes. Based on the risk distribution defined by the current model (**Figure 3**), this is a reasonable approach: essentially no non-carrier women reach a 10% risk 10-year threshold. However, more than 50% of carriers do not reach this threshold either, suggesting that a significant proportion of *BRCA1/2* carriers might be spared CPM. Contralateral surveillance mammography may also be avoided although detection and knowledge of recurrences may be necessary for better defined individualized follow-up and patient-tailored treatment strategies[63, 64].

CBC risk patterns and factors were identified previously in a large population-based study with 10,944 CBC of 212,630 patients from the Surveillance, Epidemiology and End Results (SEER) database diagnosed from 1990 to 2013[65]. However, SEER does not include details of endocrine treatment and chemotherapy, therapies administrated to reduce recurrences and CBCs[13, 66]. Furthermore, in this study the model was not validated or evaluated based on prediction accuracy, nor was a tool provided. Another study provided general guidelines for CPM by calculating the life-time risk of CBC based on a published systematic review of age at first BC, *BRCA1/2* gene mutation, family history of BC, ER status, ductal carcinoma in situ, and oophorectomy[34, 67]. However, the authors specified that the calculation of the CBC life-time risk should be considered only as a guide for helping clinicians to stratify patients into risk categories rather than a precise tool for the objective assessment of the risk.

Only one other prediction model (CBCrisk) has been developed and validated using data of 1,921 CBC cases and 5,763 matched controls[16]. External validation of CBCrisk of two independent datasets using 5,185 and 6,035 patients with 111 and 117 CBC assessed a discrimination between 0.61 and 0.65[17]. The discrimination of our PredictCBC model at 5 and 10 years was similar, however the geographic diversity of the studies gave a more complete overview of external validity[47]. Moreover, we showed the net benefit of our model using decision curve analysis since standard performance metrics of discrimination, calibration, sensitivity, and specificity alone are insufficient to assess the clinical utility[18, 53].

Some limitations of our study must be recognized. First, reporting of CBC was not entirely complete in all studies and information about CPM was limited in most datasets, which may have underestimated the cumulative incidence, although the overall 10-year cumulative incidence of 4.1% is in line with other data[5, 34]. Second, some women included in the Dutch studies (providing specific information on family history, *BRCA* mutation or CPM) were also present in our selection of the Netherlands Cancer Registry population. Privacy and coding issues prevented linkage at the individual patient level, but based on the hospitals from which the studies recruited, and the age and period criteria used, we calculated a maximum potential overlap of 3.4%. Third, in the United States and Australian datasets, the prediction performance was uncertain due to limited sample size and missing values. Moreover, some important predictors such as family history and especially *BRCA* mutation status were only available in a subset of the women (from familial- and unselected hospital-based studies) and patients with data on *BRCA* mutation status might have been insufficiently represented for tested populations and further development and validation of PredictCBC-1A will be necessary. However, although *BRCA1/2* mutation information was unavailable in 94% of our data, the approach of the imputation led to consistently good performing models[68-70]. The remaining factors were

quite complete: ~79% of patients had at most one missing factor, which provided good imputation diagnostic performances. Since most BC patients are not currently tested in the clinical practice for *BRCA1/2* mutations, we assessed the clinical utility of PredictCBC version 1B to provide individualized CBC risk estimates for first BC patients not tested for *BRCA1/2* germline mutations [60, 71]. Our PredictCBC version 1B model provides less precise estimates, but may be useful in providing general CBC risk estimates, which could steer women away from CPM or trigger *BRCA* testing.

Last but not least, adequate presentation of the risk estimates from the PredictCBC-1A and PredictCBC-1B is crucial for effective communication about CBC risk during doctor-patient consultations [72, 73]. A nomogram is an important component to communicate the risk of modern medical decision making, although it may be difficult to use and might potentially make it more difficult to interpret the risks for laymen[74] An online tool is being implemented, and a pilot-study will be conducted amongst patients and clinicians to assess how the risk estimates from PredictCBC-1A and 1B can best be visualized to facilitate communication with patients. Other factors, which were not available in our study, predict breast cancer risk and their inclusion may further improve the discrimination and clinical utility of our CBC risk model: these factors include *CHEK2* c.1100del mutation carriers, polygenic risk scores based on common genetic variants, breast density, reproductive and life-style factors such as BMI and age at menarche[75]. Additional data with complete information of *BRCA1/2* mutation should be also considered in the model upgrade to reduce uncertainty of CBC risk estimates. External validation in other studies including patients of other ethnicities, will also be important. In the meantime, our model provides a reliable basis for CBC risk counseling.

CONCLUSIONS

In conclusion we have developed and cross-validated risk prediction models for CBC (PredictCBC) based on different European-descent population and hospital-based studies. The model is reasonably calibrated and prediction accuracy is moderate. The clinical utility assessment of PredictCBC showed potential for improved risk counseling, although decision regarding CPM in the general breast cancer population remains challenging. Similar results have been found for PredictCBC version 1B, a CBC risk prediction model that calculates individualized CBC risk for first BC patients not tested for *BRCA1/2* germline mutation.

Abbreviations

AUC: Area-under-the-ROC-curve; **BC:** Breast cancer; **BCAC:** Breast Cancer Association Consortium;**BMI:** Body mass index; **CBC:** Contralateral breast cancer; **CI:** Confidence interval; **CPM:** Contralateral preventive mastectomy; **DCA:** Decision curve analysis; **ER:** Estrogen receptor; **HER2:** Human epidermal growth receptor 2; **MICE:** Multiple imputation by chained equations; **PI:** Prediction interval; **PR:** Progesterone receptor; **SEER:** Surveillance, Epidemiology and End Results; **TNM:**TNM Classification of Malignant Tumors.

Acknowledgements

We thank all individuals who took part in these studies and all researchers, clinicians, technicians and administrative staff who have enabled this work to be carried out.

ABCFS thank Maggie Angelakos, Judi Maskiell, Gillian Dite. ABCS and BOSOM thanks all the collaborating hospitals and pathology departments and many individual that made this study possible; specifically we wish to acknowledge: Annegien Broeks, Sten Cornelissen, Frans Hogervorst, Laura van 't Veer, Floor van Leeuwen, Emiel Rutgers. EMC thanks J.C. Blom-Leenheer, P.J. Bos,C.M.G. Crepin and M. van Vliet for data management. CGPS thanks staff and participants of the Copenhagen General Population Study. For the excellent technical assistance: Dorthe Uldall Andersen, Maria Birna Arnadottir, Anne Bank, Dorthe Kjeldgård Hansen. HEBCS thanks Taru A. Muranen, Kristiina Aittomäki, Karl von Smitten, Irja Erkkilä. KARMA thanks the Swedish Medical Research Counsel. LMBC thanks Gilian Peuteman, Thomas Van Brussel, EvyVanderheyden and Kathleen Corthouts. MARIE thanks Petra Seibold, Dieter Flesch-Janys, Judith Heinz, Nadia Obi, Alina Vrieling, Sabine Behrens, Ursula Eilber, Muhabbet Celik, Til Olchers and Stefan Nickels. ORIGO thanks E. Krol-Warmerdam, and J. Blom for patient accrual, administering questionnaires, and managing clinical information. The authors thank the registration team of the Netherlands Comprehensive Cancer Organisation (IKNL) for the collection of data for the Netherlands Cancer Registry as well as IKNL staff for scientific advice. PBCS thanks Louise Brinton, Mark Sherman, Neonila Szeszenia-Dabrowska, Beata Peplonska, Witold Zatonski, Pei Chao, Michael Stagner. The ethical approval for the POSH study is MREC /00/6/69, UKCRN ID: 1137. We thank the SEARCH team.

Funding

This work is supported by the Alpe d'HuZes/Dutch Cancer Society (KWF Kankerbestrijding) project 6253.

BCAC is funded by Cancer Research UK [C1287/A16563, C1287/A10118], the European Union's Horizon 2020 Research and Innovation Programme (grant numbers 634935 and 633784 for BRIDGES and B-CAST respectively), and by the European Community´s Seventh Framework Programme under grant agreement number 223175 (grant number HEALTH-F2-2009-223175) (COGS). The EU Horizon 2020 Research and Innovation Programme funding source had no role in study design, data collection, data analysis, data interpretation or writing of the report.

The Australian Breast Cancer Family Study (ABCFS) was supported by grant UM1 CA164920 from the National Cancer Institute (USA). The ABCFS was also supported by the National Health and Medical Research Council of Australia, the New South Wales Cancer Council, the Victorian Health Promotion Foundation (Australia) and the Victorian Breast Cancer Research Consortium. J.L.H. is a National Health and Medical Research Council (NHMRC) Senior Principal Research Fellow. M.C.S. is a NHMRC Senior Research Fellow. The ABCS study was supported by the Dutch Cancer Society [grants NKI 2007-3839; 2009 4363]. The work of the BBCC was partly funded by ELAN-Fond of the University Hospital of Erlangen. BOSOM was supported by the Dutch Cancer Society grant numbers DCS-NKI 2001-2423, DCS-NKI 2007-3839, and DCSNKI 2009-4363; the Cancer Genomics Initiative; and notary office Spier & Hazenberg for the coding procedure. The EMC was supported by grants from Alpe d'HuZes/Dutch Cancer Society NKI2013-6253 and from Pink Ribbon 2012.WO39.C143. The HEBCS was financially supported by the Helsinki University Hospital Research Fund, the Finnish Cancer Society, and the Sigrid Juselius Foundation.

Financial support for KARBAC was provided through the regional agreement on medical training and clinical research (ALF) between Stockholm County Council and Karolinska Institutet, the Swedish Cancer Society, The Gustav V Jubilee foundation and Bert von Kantzows foundation. The KARMA study was supported by Märit and Hans Rausings Initiative Against Breast Cancer. LMBC is supported by the 'Stichting tegen Kanker'. The MARIE study was supported by the Deutsche Krebshilfe e.V. [70-2892-BR I, 106332, 108253, 108419, 110826, 110828], the Hamburg Cancer Society, the German Cancer Research Center (DKFZ) and the Federal Ministry of Education and Research (BMBF) Germany [01KH0402]. MEC was support by NIH grants CA63464, CA54281, CA098758, CA132839 and CA164973. The ORIGO study was supported by the Dutch Cancer Society (RUL 1997-1505) and the Biobanking and Biomolecular Resources Research Infrastructure (BBMRI-NL CP16). The PBCS was funded by Intramural Research Funds of the National Cancer Institute, Department of Health and Human Services, USA. Genotyping for PLCO was supported by the Intramural Research Program of the National Institutes of Health, NCI, Division of Cancer Epidemiology and Genetics. The POSH study is funded by Cancer Research UK (grants C1275/A11699, C1275/C22524, C1275/A19187, C1275/A15956 and Breast Cancer Campaign 2010PR62, 2013PR044. PROCAS is funded from NIHR grant PGfAR 0707-10031. SEARCH is funded by Cancer Research UK [C490/A10124, C490/A16561] and supported by the UK National Institute for Health Research Biomedical Research Centre at the University of Cambridge. SKKDKFZS is supported by the DKFZ. The SZBCS (Szczecin Breast Cancer Study) was supported by Grant PBZ_KBN_122/P05/2004 and The National Centre for Research and Development (NCBR) within the framework of the international ERA-NET TRANSAN JTC 2012 application no. Cancer 12-054 (Contract No. ERA-NET-TRANSCAN / 07/2014).

Availability of data and materials

All data relevant to this report are included in this published article and its supplementary information files. The datasets analyzed during the current study are not publicly available due to protection of participant privacy and confidentiality, and ownership of the contributing institutions, but may be made available in anonymized form via the corresponding author on reasonable request and after approval of the involved institutions.

Authors' contributions

MKS and MJH conceived the study in collaboration with EWS and MH. DG performed the statistical analysis. DG, MKS, MJH, EWS and MH interpreted the results and drafted the manuscript. MAA, DA, CB, SEB, MKB, MB, JCC, KC, PD,AMD, DFE, DME, PAF, JF,HF,MGC,LK, CAH, PH, UH, JLH, AG, AJ1, AJ2, RK, IK, DL, LLM, AL, JL, MM, LM, HN, HSAO, SP, PDPP, MS, SS, VTHBMS, MCS, WJT, RAEMT, AJvB, CHMvD, FEvL, CvO, LJvV, QW, CW, PJW contributed to critical revision and editing of the final version of the manuscript for publication. All authors were involved in data generation or provision, and read and approved the final manuscript.

Ethics approval and consent to participate

Each study was approved by its institutional ethical review board.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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SUPPLEMENTARY MATERIALS

1. Data and patient selection

For this study we used data from five main sources available from national and international collaborations including nationwide registry data, as well as studies with more detailed information on relevant prediction factors[1-5]. Briefly, the five main sources were: (1) The Breast Cancer Association Consortium (BCAC), which is an international consortium of 102 studies comprising 182,898 patients (data version: January 2017) with a primary breast cancer (BC) diagnosed between 1939 and 2016[1]; (2) The Amsterdam Breast Cancer Study (ABCS) containing 2,390 patients diagnosed with a first BC at the Netherlands Cancer Institute – Antoni van Leeuwenhoek (NKI-AVL) hospital in Amsterdam from 2003 to 2013[2]; (3) The Breast Cancer Outcome Study of Mutation carriers (BOSOM), which is a Dutch consecutive series of 7,106 patients with invasive BC treated for their primary BC in ten centers throughout the Netherlands between 1970 and 2003; in this study 94% of patients were genotyped for *BRCA1/2* germline mutations[3]; (4) The Erasmus Medical Center (EMC) study containing patients diagnosed with BC between 1989 and 2013 who were treated at the EMC in Rotterdam; for this study, complete follow-up was obtained for 3,483 patients that had been diagnosed between 2000 and 2009; (5) The Netherlands Cancer Registry (NCR), which is an ongoing nationwide population-based data registry of all newly diagnosed cancer patients in the Netherlands since 1989[4]. We included patients diagnosed between 2003 and 2010, a period for which sufficient follow-up and receptor status information were provided[4, 5]. The eligibility criteria applied in each data source is reported in **Table S1**. Data were harmonized by recoding each of the main datasets by the responsible data managers according to a standardized data dictionary. We performed checks for data consistency and validity centrally.

We extracted the following information: *BRCA1/2* germline mutation, family history (first degree) of primary BC, and regarding primary BC diagnosis: age, nodal status, size, grade, morphology, estrogen-receptor (ER) status, progesterone-receptor (PR), human epidermal growth factor receptor 2 (HER2) status, administration of adjuvant or neoadjuvant chemotherapy, adjuvant endocrine therapy, adjuvant trastuzumab therapy, radiotherapy. We excluded PR status and TNM stage of the primary BC due to collinearity with ER status and the size of the primary tumor, respectively. In the current clinical practice, only patients with ER-positive tumors receive endocrine therapy and only patients with HER2-positive tumors receive trastuzumab; these co-occurrences were considered in the model by using composite categorical variables. A description of the studies included in the analyses is provided in **Table S2**. Follow-up started three months after invasive first primary BC diagnosis, in order to exclude synchronous CBCs, and ended at date of CBC, distant metastasis (but not at loco-regional relapse), CPM, or last date of follow-up (due to death, being lost to follow-up, or end of study), whichever

occurred first. We considered that after loco-regional relapse, a woman would be still at risk for CBC as treatment for loco-regional relapse would not affect the contralateral breast cancer (CBC) unless adjuvant systemic treatment was given. Distant metastasis was considered as a competing risk because most of the patients receive systemic therapies after developing distant metastasis.

Table S1. Data source flowchart.

	Source of data				
	ABCS	**BCAC‡**	**BOSOM**	**EMC**	**NCR**
Number of patients	2,390	182,898	7,105	3,483	94,600
Eligibility criteria, *number of patients excluded*					
Studies from Asian countries	-	7,348	-	-	-
Patients of non-European descent	-	46,670	-	-	-
Year of PBC diagnosis before 1990	-	3,358	3,126	-	-
Year of PBC diagnosis missing	-	26,291	-	-	-
PBC stage 0	122	34	2	-	-
PBC stage IV	94	1,675	104	-	4,569
Patients did not undergo surgery	24	1,138	43	5	5,174
Number of eligible patients	2,150	96,384	3,830	3,478	84,857
No follow-up or follow-up less than 3 months	171	13,144	70	88	1,719
Familiar breast cancer studies	-	4,635	-	-	-
Studies with less than 10 CBC events	-	38,116	-	-	-
Number of patients included in the analysis (number of patients with CBC)	1,979 (19)	40,489 (707)	3,760 (288)	3,390 (221)	83,138 (3,447)
Total number of patients included in the analysis (number of CBC)	132,756 (4,682 of which 3,974 invasive and 708 *in-situ*)				

Abbreviations: ABCS: Amsterdam Breast Cancer Study; BCAC: Breast Cancer Association Consortium. ‡BCAC is composed of 102 studies world-wide. The 40,489 patients selected for the analysis came from 16 studies.; BOSOM: Breast Cancer Outcome Study of Mutation carriers; EMC: Erasmus Medical Center; NCR: Netherlands Cancer Registry; PBC: primary breast cancer; CBC: contralateral breast cancer

Table S2: see online material

Age at first primary BC seemed to have a non-linear relationship with CBC; using splines we observed that CBC risk increased with age till around 50 years old and declined afterwards; see **Figure S1**. Therefore, we used a linear spline with a knot at 50 years in the prediction model. The use of this linear spline was a good compromise to address the non-linear relationship between CBC risk and age across the different baseline risks in all the studies, with different age distributions and selections (one study included only women aged under 50 years). Moreover, the observed non-linear relationship resembled the shape of age-related BC incidence curves with an increased risk until menopausal age followed by a decrease (Clemmensen's hook)[6].

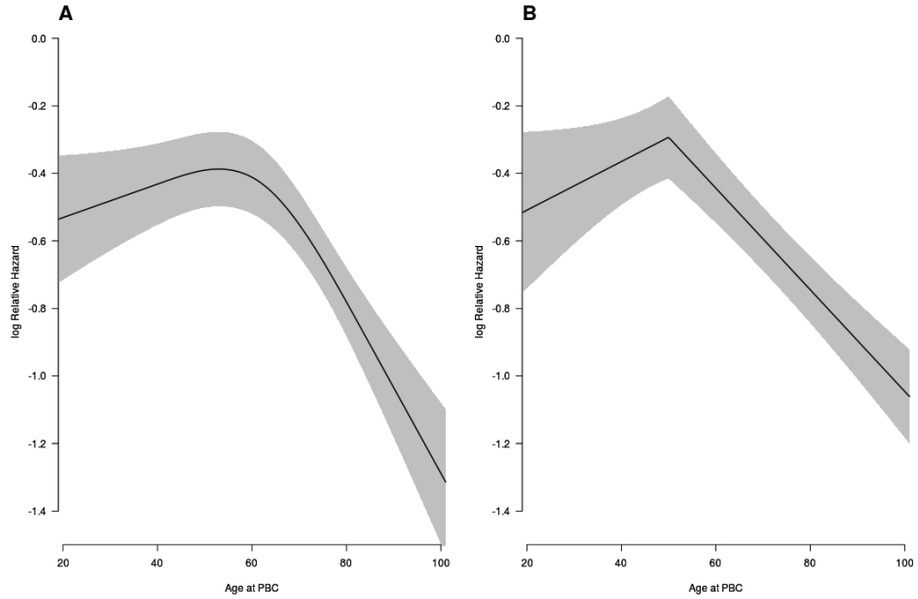

Figure S1: Graphical assessment of non-linear relationship of age with contralateral breast cancer risk.
A non-linear relationship between age at first primary breast cancer (x-axis) and the log relative hazard of contralateral breast cancer (y-axis) is shown. Panel A shows a restricted cubic spline with three knots. Panel B shows a linear spline with one knot located at 50 years. The curve gray area indicates the corresponding 95% confidence intervals. Both curves were estimated from a multivariable subdistributional hazard model adjusted for the variables used for the risk prediction considering death for any causes and distant metastasis as a competing risk.

2. Multiple imputation of missing values

The percentage of missing values across the predictors varied between 5.1% and 94.2% for morphology of first primary BC and *BRCA* mutation, respectively. In the individual patient data (IPD), both sporadic and systematic missing may occur. The former are missing values within a study, the latter are values missing for all individuals within a particular study[7-9].

For our analyses, we used ten imputed datasets based on the multiple imputation chained equations (MICE) using 50 iterations. The visit sequence of the variables was in ascending order of the number of missing values. This technique improves the accuracy and the statistical power assuming missing is at random (MAR). In the imputation procedure, we also used the year of first primary BC diagnosis since this information provides a better correlation structure among covariates used as predictors in the imputation model. Since there were systematic missing data, we used the imputation model based on the stratified multiple imputation strategy (SMI). In this approach, the variable identifying

the study was used as covariate to improve substantially the imputation especially for the systematic missing predictors that might occur in the individual patient data (IPD) from multiple studies[9]. Continuous, binary and multiple categorical variables were imputed using predictive mean matching, binary and polytomous logistic regression, respectively. Time-to-event outcome defined as time to contralateral breast, time to death, and time to distant metastasis were included in the imputation process through the Nelson-Aalen cumulative hazard estimator[10]. For every variable with missing data, every imputation model selects predictors based on correlation structure underlying the data. We recoded the variables chemotherapy and morphology after imputation. In particular, information about neoadjuvant and adjuvant chemotherapy were separately imputed. Then, we created a chemotherapy variable by combining the variables for neoadjuvant and adjuvant chemotherapy in every imputed dataset. Morphology of primary tumor was imputed by keeping all original categories ('Lobular', 'Ductal', 'Mixed' and 'Other'). After multiple imputation, we created two categories 'Lobular including mixed' and 'Ductal including other' to address possible overfitting due to the small samples of 'Mixed' and 'Other' categories. Since in current clinical practice, only estrogen receptor (ER) positive patients receive endocrine therapy and only human epidermal growth factor receptor 2 (HER2) positive patients receive trastuzumab, composite categorical factors of ER and endocrine therapy and of HER2 and trastuzumab therapy were considered in the model building. However, in our data, 2% of patients with 70 CBC events were coded as ER-negative treated with endocrine therapy and 0.2% of patients with 7 CBC events were coded as HER2-negative treated with trastuzumab therapy. In every imputed dataset, we recoded those patients as ER-positive treated with endocrine treatment and HER2-positive treated with trastuzumab since the largest proportion of patients (53%) were ER-positive treated with endocrine therapy and 82% were HER2-positive treated with trastuzumab in the complete data.

We used the R package mice (version 2.46.0) to impute our data and combine the estimates using Rubin's rules.

3. Complete case analysis

When a missing data pattern is completely at random (MCAR), imputation of missing data is not necessary. Therefore, descriptive analyses were performed to check whether the missing data pattern was MCAR. For completeness, the patients and first primary breast cancer characteristics and results of the multivariable subdistributional hazard model based on the case set with complete data are shown in **Table S3** and **Table S4,** respectively. The prediction performance of the risk prediction model was not investigated since in the case set with complete data all cases came from one geographic area (Western Europe) and the number of CBC event did not reach the number of events required for an external validation.

Table S3: Patients and first primary breast cancer characteristics used in the contralateral breast cancer risk prediction model in the complete case and all case analyses.

Factors at primary breast cancer		N	%
		132,756	**100.0**
Age, *years*			
	Median (range)	57 (18 - 101)	
	Missing	-	
Family history			
	Yes	5,959	19.5
	No	24,582	80.5
	Missing	102,215	-
BRCA mutation			
	BRCA1	333	4.3
	BRCA2	167	2.2
	Non carrier	7,204	93.5
	Missing	125,052	-
Nodal status			
	Positive	48,979	39.1
	Negative	76,356	60.9
	Missing	7,421	-
Tumor size, *cm*			
	≤ 2	75,849	60.8
	(2-5]	43,075	34.5
	> 5	5,916	4.7
	Missing	7,916	-
Tumor grade			
	well differentiated	25,271	21.7
	moderately differentiated	53,385	45.7
	poorly/undifferentiated	38,045	32.6
	Missing	16,055	-
ER status			
	Positive	97,460	80.5
	Negative	23,625	19.5
	Missing	11,671	-
HER2 status			
	Positive	15,401	17.4
	Negative	72,891	82.6
	Missing	44,464	-
Morphology			
	Ductal	96,561	76.6
	Lobular	14,681	11.7
	Mixed	4,982	4.0
	Other	9,780	7.8
	Missing	6,752	-
Adjuvant chemotherapy			
	Yes	46,868	38.2
	No	75,785	61.8
	Missing	10,103	-
Neoadjuvant chemotherapy			
	Yes	7,213	6.0
	No	112,267	94.0
	Missing	13,276	-

Table S3: Continued

Factors at primary breast cancer		N	%
		132,756	100.0
Endocrine adjuvant therapy			
	Yes	65,959	54.1
	No	56,055	45.9
	Missing	10,742	-
Trastuzumab adjuvant therapy			
	Yes	6,875	6.7
	No	9,6324	93.3
	Missing	29,557	-
Radiation in the breast			
	Yes	85,029	69.5
	No	37,237	30.5
	Missing	10,490	-
CBC cumulative incidence, *%*			
	5-year (95%CI)	2.1 (2.1 - 2.2)	
	10-year (95%CI)	4.1 (4.0 - 4.3)	

Abbreviations:
PBC: primary breast cancer; ER: estrogen-receptor; HER2: human epidermal growth factor receptor 2; CBC: contralateral breast cancer; CI: confidence interval.

Table S4: Results of multivariable subdistributional hazard model using the complete case dataset.

Factor (categories) at primary breast cancer	Multivariable analysis	
	sHR	95% CI
Age, *years*	1.48[a]	0.73 – 3.00[a]
Family history (yes versus no)	1.36	0.69 - 2.70
BRCA mutation		
BRCA1 versus non-carrier	5.28	2.13 - 13.10
BRCA2 versus non-carrier	2.30	0.50 - 10.51
Nodal status (positive versus negative)	1.37	0.56 - 3.34
Tumor size, *cm*		
(2,5] versus ≤ 2	0.57	0.22 - 1.47
> 5 versus ≤ 2	3.53	1.10 - 11.34
Morphology (lobular including mixed versus ductal including other)	0.99	0.33 - 2.88
Grade		
Moderately differentiated versus well differentiated	0.91	0.28 - 2.88
Poorly differentiated versus well differentiated	0.84	0.23 - 3.04
Chemotherapy (yes versus no)	0.38	0.16 – 0.89
Radiotherapy to the breast (yes versus no)	1.26	0.56 - 2.83
ER (positive or negative) / endocrine therapy (yes or no)		
negative/no versus positive/yes	1.42	0.53 - 3.77
positive/no versus positive/yes	2.38	0.90 - 6.31
HER2 (positive or negative) / trastuzumab therapy (yes or no)		
negative/no versus positive/yes	0.71	0.22 - 2.36
positive/no versus positive/yes	0.32	0.07 - 1.46

Abbreviations:
sHR: subdistributional hazard ratio; CI: confidence interval; ER: estrogen receptor; HER2: human epidermal growth factor receptor 2;
[a] Age was parameterized as a linear spline at 50. For presentation purposes, we here provide the sHR for the 75th versus the 25th percentile.

4. Model diagnostics and baseline recalibration

For the multivariable model, we checked the assumption of proportional subdistribution hazards graphically using Schoenfield residuals. Heterogeneity of baseline risks between studies was taken into account using the study as a stratification term. We estimated the cumulative incidence at 5- and 10- year using the baseline hazard of the Netherlands Cancer Registry (NCR) dataset to improve the model calibration, since this is our largest cohort (67% of the data) and is based on complete incidence data thus provides a representative cumulative incidence of CBC (4.6% at 10 years). The stratified model and the application of the Rubin's rules took into account both the between study and between imputation variation.

5. Leave-one-study-out cross-validation

We used leave-one-study-out cross-validation (also known as an internal-external validation), in which a model for predicting CBC risk is developed in all studies except one whose external validity is evaluated (every study is excluded once in this process). For the studies where the number of CBC events was insufficient for external validation, we used the geographic area as a unit of splitting. For time-to-event outcomes at least 100 events per study are required for external validation[11]. The geographic area corresponding to every study is shown in **Table S5**.

Table S5: List of BCAC studies (including ABCS source) with the corresponding country and geographic area. For studies in which the number of contralateral breast cancer events was insufficient for external validation, the geographic area was used.

Study	Country	Geographic area or study
ABCS	Netherlands	Europe - Other
ABCFS	Australia	United States and Australia
BBCC	Germany	Europe - Other
CGPS	Denmark	Europe - Scandinavia
HEBCS	Finland	Europe - Scandinavia
KARBAC	Sweden	Europe - Scandinavia
KARMA	Sweden	Europe - Scandinavia
LMBC	Belgium	Europe - Other
MARIE	Germany	Europe - Other
MEC	United States	United States and Australia
ORIGO	Netherlands	Europe - Other
PBCS	Poland	Europe - Other
PKARMA	Sweden	Europe - Scandinavia
POSH	United Kingdom	Europe - United Kingdom
SEARCH	United Kingdom	Europe - United Kingdom
SKKDKFZS	Germany	Europe - Other
SZBCS	Poland	Europe - Other

Table S6: see online material

We evaluated the discrimination accuracy using the time-dependent area under the curve (AUC) at 5- and 10-year. The Inverse Probability of Censoring Weighting (IPCW) was computed to estimate of cumulative/dynamic time-dependent AUCs[12]. Since the mortality and distant metastasis were competing risks, a control was defined as a subject not experiencing a CBC at 5- and 10-year, respectively. The AUC estimate and the corresponding confidence intervals were computed by bootstrapping 100 times every imputed dataset in each validation study. The AUCs and the corresponding confidence intervals were pooled using Rubin's rules.

We did not consider delayed-entry patients (with prevalent BC) to evaluate the discrimination accuracy of the prediction models since no standard performance measures are currently available in the statistical literature to account for left-truncated follow-up time. In our study the median of delayed entry was 0.6 years.

We assessed the calibration of the models using calibration-in-the-large, calibration slope, and calibration plots per study[13]. Calibration plots report the predicted probabilities on the x-axis and the observed probabilities on the y-axis. For time-to-event data, this plot can be generated at multiple time points. To reproduce the nomogram building, we used the predicted and observed cumulative incidence of 5- and 10-year as time points for the calibration plots. The observed and predicted outcomes are divided by quartiles of predicted values. In case of good overall calibration, all points in a calibration plot are near the 45-degree line starting at the origin (0,0). If points are below the 45-degree line, models overestimate the observed risk (overfitting). If points are above the 45-degree line, the model underestimates the observed risk (underfitting). In each validation study, calibration slopes and predicted probabilities at 5 and 10 years were calculated in every imputed dataset. Then, for each validation study, calibration slopes and the predicted probabilities were pooled using Rubin's rules. Calibration plots at 5- and 10-year are shown in **Figures S2 and S3,** respectively.

6. Clinical utility

The decision curve analysis combines the direct applicability of the decision-analytic methods with the mathematical simplicity of accuracy metrics[14]. The mathematical background of the net benefit calculation was originally developed by Peirce in 1884[15]. More recently, other publications expanded this work and proposed and gave emphasis why the net benefit measures should be used beyond measures of discrimination and calibration to assess the accuracy of prediction models[16].
The net benefit (NB) is calculated as:

$$NB = \frac{TP}{n} - \frac{FP}{n}\left(\frac{p_t}{1-p_t}\right)$$

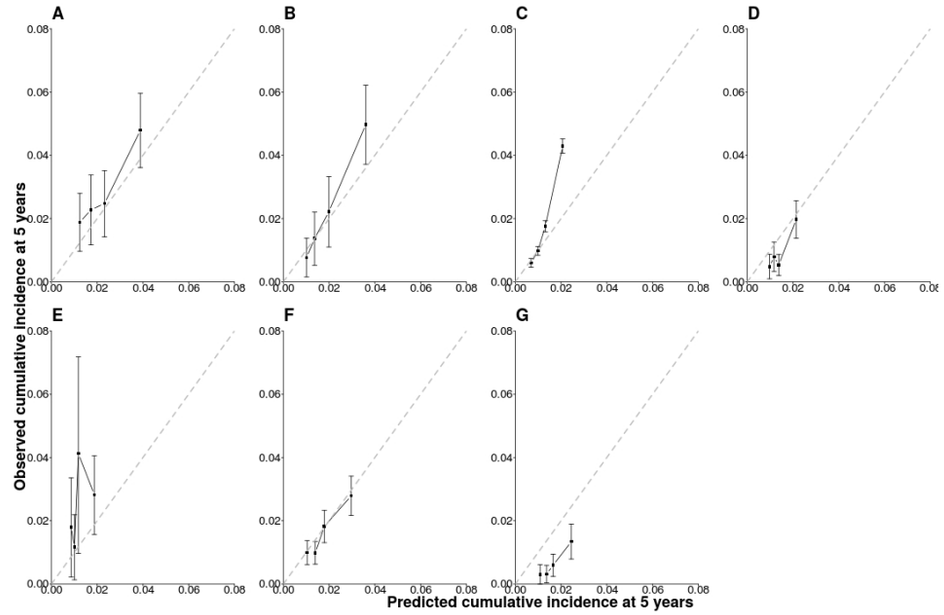

Figure S2: Visual assessment of calibration through calibration plots in the internal-external cross-validation at 5 years for the contralateral breast cancer risk model with *BRCA* mutation information. The x-axis represents the predicted cumulative incidence of contralateral breast cancer at 5 years and the y-axis the observed cumulative incidence at 5 years. The black dots indicate the calibration for quartiles of predicted values. Vertical black bars indicate the 95% confidence intervals. The dashed gray line indicates perfect overall calibration. Each panel indicates a validation in one of the datasets. Panel A: Netherlands - BOSOM; Panel B: Netherlands - EMC; Panel C: Netherlands - NCR; Panel D: Europe – Scandinavia; Panel E: United States and Australia; Panel F: Europe – Other; Panel G: Europe – United Kingdom.

Where n is the total sample size *TP* = true positive counts; *FP* = false positive counts; p_t = risk threshold that defines the high risk and low risk patients. The ratio $\frac{p_t}{1-p_t}$ represents the relative weight of the harm of unnecessary contralateral preventive mastectomies (CPM) versus the benefit of CBC patients who truly need the surgery. To draw the decision curve, the net benefit is calculated for different values of p_t.

The risk thresholds and the calculation of the true positives and false negatives in case of censored data with competing risks are defined as:

$$TP = \{I(t)|X = 1\} \cdot P(X = 1) \cdot n$$
$$FP = \{1 - I(t)|X = 1\} \cdot P(X = 1) \cdot n$$

Where:
n = total number of BC patients;
I(t) = cumulative incidence of CBC predicted by the prediction model at time *t*;

$$X = \begin{cases} 1\ predicted\ \ cumulative\ incidence\ at\ time\ t\ \geq\ p_t \\ 0\ predicted\ \ cumulative\ incidenceat\ time\ t\ <\ p_t \end{cases}$$

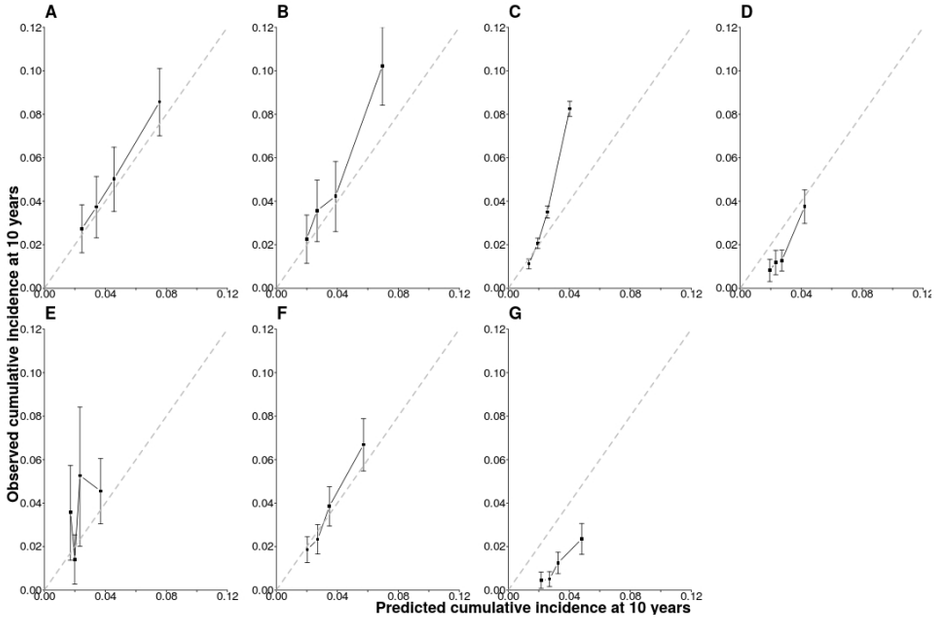

Figure S3: Visual assessment of calibration through calibration plots in the internal-external cross-validation at 10 years for the contralateral breast cancer risk model with *BRCA* mutation information. The x-axis represents the predicted cumulative incidence of contralateral breast cancer at 10 years and the y-axis the observed cumulative incidence at 10 years. The black dots indicate the calibration for quartiles of predicted values. Vertical black bars indicate the 95% confidence intervals. The dashed gray line indicates perfect overall calibration. Each panel indicates a validation in one of the datasets. Panel A: Netherlands - BOSOM; Panel B: Netherlands - EMC; Panel C: Netherlands - NCR; Panel D: Europe – Scandinavia; Panel E: United States and Australia; Panel F: Europe – Other; Panel G: Europe – United Kingdom.

More mathematical details have been provided by Vickers in 2008 and Kerr in 2016[17, 18]. The landmark time *t* was set to 5 and 10 years since the prediction model provided the estimated cumulative incidence at 5 and 10 years.

Although discrimination measures such as sensitivity, specificity, Area Under the Curve (AUC), and c-statistic and calibration measures cannot be used to assess the clinical utility of a prediction model, net benefit is larger for more discriminating models and decrease with poor calibration[19]. Referring to our model, the reduction in the number of unnecessary CPM per 1,000 patients without a decrease in the number of patients who correctly received the surgery is calculated as:

$$(net\ benefit\ of\ the\ model - net\ benefit\ of\ treat\ all)/(\ pt\ /(1 - pt))\ \times\ 1{,}000$$

For example, at a risk threshold of 10% the difference between the net benefit of the prediction model and the net benefit of treat all was 0.0179, the number of avoidable unnecessary CPM would be [0.0179/(0.10/0.90)] = 0.1611 x 1000 = 161.1 per 1,000 patients.

Results of the decision curve analysis that were not reported in Table 2, are reported in **Table S7.** The utilization of 5-year CBC risk prediction in terms of net benefit showed that for some risk thresholds (between 1.5–4.5%), the prediction model might be clinically useful to avoid unnecessary CPM among *BRCA1* patients and to counsel necessary CPM among non-carriers. As an example, if a clinician finds it acceptable to perform around 21 unnecessary CPM to prevent one CBC (one necessary CPM), a risk threshold of 4.5% may be used to define high and low risk *BRCA1/2* patients based on the absolute 5-year CBC risk prediction estimated by the model. In this scenario, approximately 163 CPMs per 1,000 patients may be avoided using the model compared to counseling CPM to all *BRCA1/2* carriers. Similarly, if unnecessarily performing a CPM in 39 patients would be acceptable to prevent one CBC, a risk threshold of 2.5% may be used to define high and low risk non-carriers; and this would include around necessary 491 CPMs per 1,000 patients. The decision curves in **Figures S4** provide a comprehensive overview of the net benefit for a range of harm-benefit thresholds at 5-year CBC risk.

Table S7: Clinical utility of the 5-year contralateral breast cancer risk prediction model. At the same probability threshold, the net benefit is exemplified in *BRCA1/2* mutation carriers (for avoiding unnecessary CPM) and non-carriers (performing necessary CPM).

		BRCA1/2 mutation carriers		Non-carriers	
Probability threshold p_t (%)	Unnecessary CPMs needed to prevent a CBC*	Net benefit versus treat all patients with CPM (per 1000)	Avoided unnecessary CPMs per 1000 patients	Net benefit versus treat none (per 1000)	Performed necessary CPMs per 1000 patients
1.5	65.7	0.0	0.0	3.3	216.7
2.5	39.0	0.1	3.9	12.6	491.4
3.5	27.6	2.3	63.4	0.1	2.8
4.5	21.2	7.7	163.4	0.0	0.0

CPM: contralateral preventive mastectomy; CBC: contralateral breast cancer;
* The number of unnecessary contralateral mastectomies needed to prevent a CBCis calculated by: $(1\text{-}p_t)/p_t$

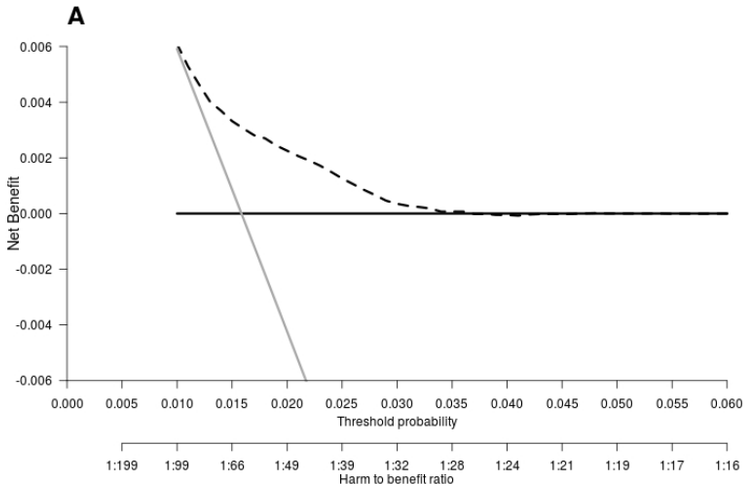

Figure S4: Decision curve analysis at 5 years for the contralateral breast cancer risk model including *BRCA1/2* mutation information.
Panel A shows the decision curve to determine the net benefit of the estimated 5-year predicted contralateral breast cancer (CBC) cumulative incidence for patients without a *BRCA1/2* gene mutation using the prediction model (dotted black line) compared to not treating any patients with contralateral preventive mastectomy (CPM) (black solid line). Panel B shows the decision curve to determine the net benefit of the estimated 5-year predicted CBC cumulative incidence for *BRCA1/2* mutation carriers using the prediction model (dotted black line) versus treating (or at least counseling) all patients (grey solid line). The y-axis measures net benefit, which is calculated by summing the benefits (true positives, i.e., patients with a CBC who needed a CPM) and subtracting the harms (false positives, i.e., patients with CPM who do not need it). The latter are weighted by a factor related to the relative harm of a non-prevented CBC versus an unnecessary CPM. The factor is derived from the threshold probability to develop a CBC at 5 years at which a patient would opt for CPM (e.g. 4.5%). The x-axis represents the threshold probability. Using a threshold probability of 4.5% implicitly means that CPM in 22 patients of whom one would develop a CBC if untreated is acceptable (21 unnecessary CPMs, harm to benefit ratio 1:21).

7. Formula to estimate the contralateral breast cancer risk

Our developed model is a subdistributional proportional hazard Fine and Gray model. The estimated cumulative incidence of CBC was estimated using the following formula:

$$F(t) = 1 - \left\{[S_0(t)]^{\exp(\boldsymbol{LP})}\right\}$$

Where *t* is the time (in years) since primary BC, *F* (*t*) is the cumulative incidence of CBC and $S_0(t)$ is the probability to survive beyond for baseline covariate values. The baseline survival estimates according to the model and time are:

$S_0(5) = 0.984$
$S_0(10) = 0.968$

And

Linear Predictor (LP) =

– 0.223 + 0.007× Age – 0.023 × Age' + 0.303 × I[Family history = Yes] + 1.304 × I[*BRCA* = *BRCA1*] + 0.941 × I[*BRCA* = *BRCA2*] – 0.142 × I[Nodal status = positive] – 0.047 × I[Size of PBC = (2,5] *cm*] + 0.128 × I[Size of PBC = greater than 5 *cm*] + 0.209 × I[Morphology of PBC = lobular including mixed] – 0.120× I[Grade of PBC = moderately differentiated] – 0.291 × I[Grade of PBC = poorly/undifferentiated]– 0.266 × I[Chemotherapy = yes] + 0.009 × I[Radiotherapy to the breast = yes] + 0.356 × I[ER-negative without endocrine therapy] + 0.559 × I[ER-positive without endocrine therapy]+ 0.082 × I[HER2-negative without trastuzumab] – 0.005 × I[HER2-positive without trastuzumab]

Where Age' = max(Age – 50, 0)

8. Results of the prediction model without BRCA mutation

Because a patient may not have been tested for the *BRCA* gene mutations, this information may not be available before or on the day of first primary BC diagnosis or treatment decisions. Moreover, information about *BRCA* mutations was largely missing in the databases we used. Thus, we also developed and validated a CBC prediction model without *BRCA* mutations to also provide an individualized risk prediction tool for patients not tested. Results of the risk prediction model in terms of relative subdistributional hazard ratio (sHRSs) and the corresponding 95% confidence intervals (CI) for patients not tested for *BRCA* gene mutations are provided in **Table S8**.

The assessments of prediction performance are shown in **Figures S5, S6, and S7.** The discrimination accuracy at 5 years was 0.59 (95% CI: 0.54 – 0.63; 95% prediction interval (PI): 0.46 – 0.71) and at 10 years was 0.59 (95% CI: 0.56 – 0.62; 95% PI: 0.52 – 0.66), as shown in **Figure S5**. The calibration-in-the-large was -0.17 (95% CI: -0.72 – 0.38; 95% PI: -1.70– 1.36), as shown in the **Figure S5 panel C;** and calibration slope was 0.81 (95% CI: 0.63 – 0.99; 95% PI: 0.50 – 1.12) in the leave-one-study-out cross-validation, as shown

in **Figure S5 panel D**. The calibration plots at 5- and 10-year are reported in **Figures S6 and S7**, respectively.

Table S8: Results of multivariable subdistributional hazard model for breast cancer patients without *BRCA* mutations.

Factor (category) at primary breast cancer	Multivariable analysis	
	sHR	95% CI
Age, *years*	0.61[a]	0.56-0.66[a]
Family history (yes versus no)	1.60	1.50 - 1.71
Nodal status(positive versus negative)	0.87	0.80 - 0.93
Tumor size, *cm*		
(2,5] versus ≤ 2	0.96	0.89 - 1.03
> 5 versus ≤ 2	1.11	0.97 - 1.28
Morphology (lobular including mixed versus ductal including other)	1.20	1.10 - 1.30
Grade		
Moderately differentiated versus well differentiated	0.97	0.90 - 1.04
Poorly differentiated versus well differentiated	0.87	0.79 - 0.96
Chemotherapy (yes versus no)	0.78	0.71 - 0.85
Radiation of the breast (yes versus no)	0.97	0.90 - 1.03
ER (positive or negative) / endocrine therapy (yes or no)		
negative/no versus positive/yes	1.67	1.54 - 1.84
positive/no versus positive/yes	1.81	1.67 - 1.96
HER2 (positive or negative) / trastuzumab therapy (yes or no)		
negative/no versus positive/yes	1.26	1.08 - 1.48
positive/no versus positive/yes	1.08	0.91 - 1.30

Abbreviations:
sHR: subdistributional hazard ratio; CI: confidence interval; ER: estrogen receptor; HER2: human epidermal growth factor receptor 2;
[a]: Age was parameterized as a linear spline at 50. For representation purposes, we here provide the sHR for the 75th versus the 25th percentile.

Table S9. Clinical utility of the 5-year contralateral breast cancer risk prediction model in non-*BRCA* tested patients. At the same probability threshold, the net benefit is exemplified in patients with family history (for avoiding unnecessary CPM) and patients without family history (performing necessary CPM).

		Family history		No family history	
Probability threshold p_t (%)	Unnecessary CPMs needed to prevent a CBC*	Net benefit versus treat all patients with CPM (per 1000)	Avoided unnecessary CPMs per 1000 patients	Net benefit versus treat none (per 1000)	Performed necessary CPMs per 1000 patients
2.0	49.0	0.4	19.6	2.1	102.9
2.5	39.0	2.9	113.1	1.2	46.8
3.0	32.3	0.0	0.0	0.2	6.5

CPM: contralateral preventive mastectomy; CBC: contralateral breast cancer;
* The number of unnecessary contralateral preventive mastectomies needed to prevent a CBC is calculated by: $(1-p_t)/p_t$

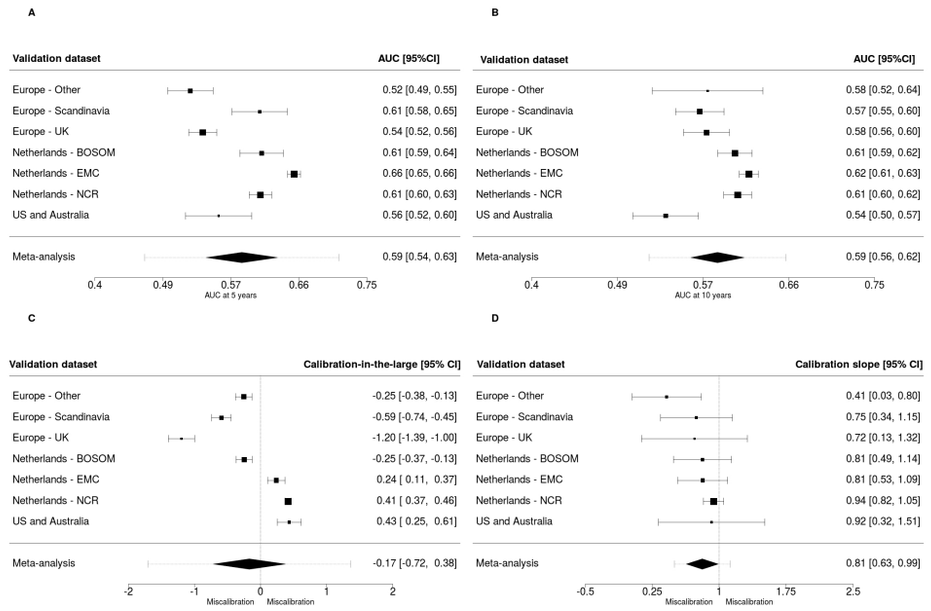

Figure S5: Results of the leave-one-study-out cross-validation for the contralateral breast cancer risk model at 5 and 10 years without *BRCA* mutation information.
Panel A and B show the discrimination accuracy assessed by a time-dependent AUC at 5 and 10 years, respectively. Panel C shows the calibration accuracy measured with calibration in-the-large. Panel D shows the calibration accuracy measured with calibration slope. The black squares indicate the estimated accuracy of the model in a single new validation study or geographic area. The black horizontal lines interval indicate the corresponding 95% confidence intervals of the estimated accuracy (interval whiskers). The black diamonds indicate the mean with the corresponding 95% confidence interval of the predictive accuracy and the dashed horizontal lines indicate the corresponding 95% prediction intervals.

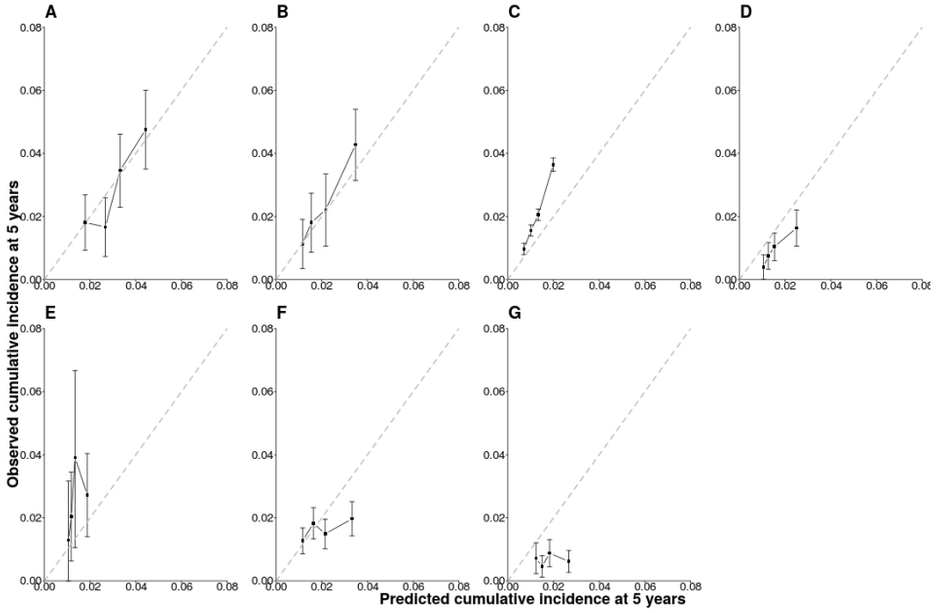

Figure S6: Visual assessment of calibration through calibration plots in the internal-external cross-validation at 5 years for the contralateral breast cancer risk model without *BRCA* gene mutation information.

The x-axis represents the predicted cumulative incidence of contralateral breast cancer at 5 years and the y-axis the observed cumulative incidence at 5 years. The black dots indicate the calibration for quartiles of predicted values. Vertical black bars indicate the 95% confidence intervals. The dashed gray line indicates perfect overall calibration. Each panel indicates a validation in one of the datasets. Panel A: Netherlands - BOSOM; Panel B: Netherlands - EMC; Panel C: Netherlands - NCR; Panel D: Europe – Scandinavia; Panel E: United States and Australia; Panel F: Europe – Other; Panel G: Europe – United Kingdom.

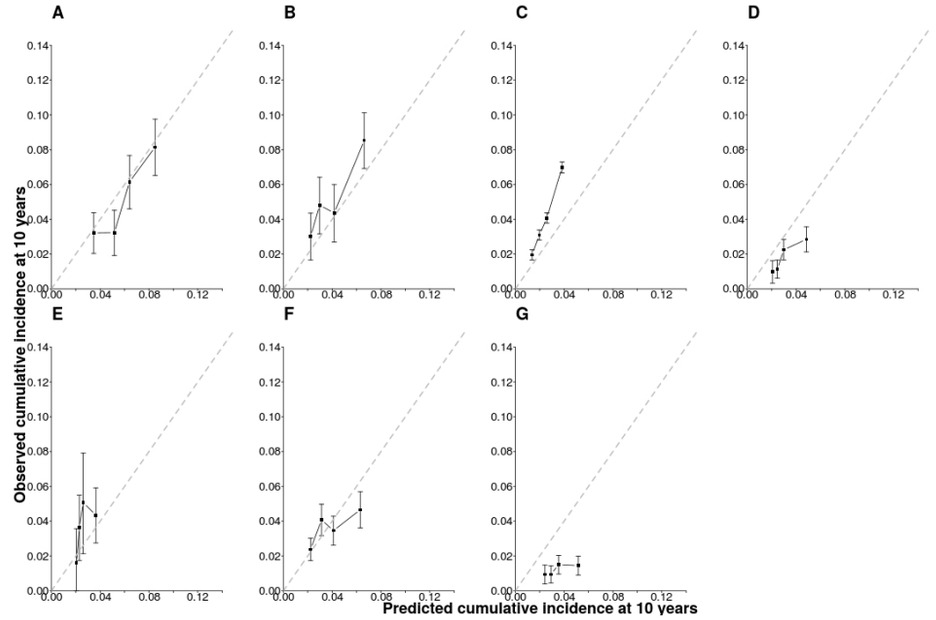

Figure S7: Visual assessment of calibration through calibration plots in the internal-external cross-validation at 10 years for the contralateral breast cancer risk model without *BRCA* gene mutation information.

The x-axis represents the predicted cumulative incidence of contralateral breast cancer at 10 years and the y-axis the observed cumulative incidence at 10 years. The black dots indicate the calibration for quartiles of predicted values. Vertical black bars indicate the 95% confidence intervals. The dashed gray line indicates perfect overall calibration. Each panel indicates a validation in one of the datasets. Panel A: Netherlands - BOSOM; Panel B: Netherlands - EMC; Panel C: Netherlands - NCR; Panel D: Europe – Scandinavia; Panel E: United States and Australia; Panel F: Europe – Other; Panel G: Europe – United Kingdom.

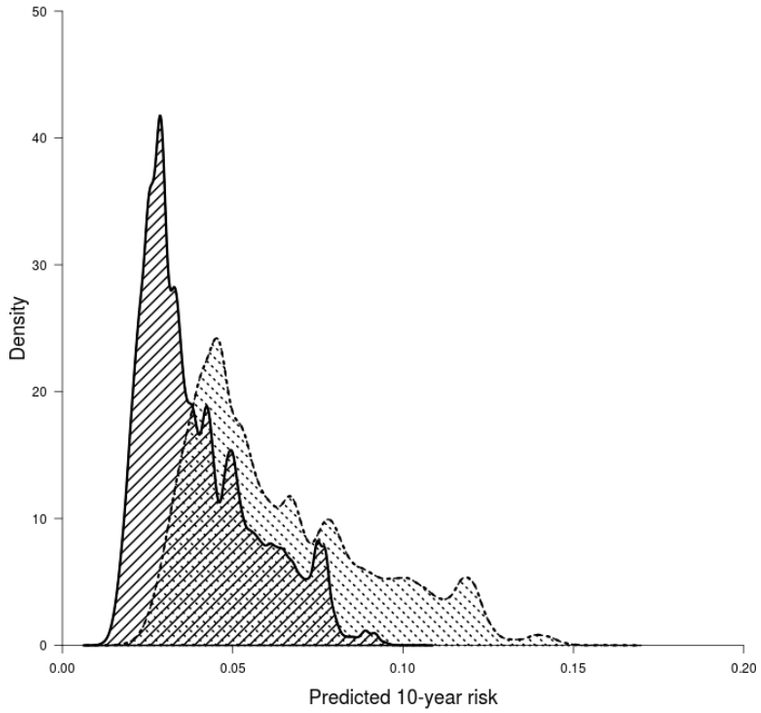

Figure S8: Density distribution of 10-year predicted absolute risk in patients with no family history (area with black lines) and patients with a family history (area with dashed lines).

The utilization of 10-year CBC risk prediction in terms of net benefit showed that for some risk thresholds (between 3.5–5.5%), the prediction model might be clinically useful to avoid unnecessary CPM among patients with family history and to counsel necessary CPM among patients without first-degree relatives with BC. For example, if a clinician finds it acceptable to perform around 21 unnecessary CPM to prevent one CBC, a risk threshold of 4.5% may be used to define high and low risk patients with family history based on the absolute 10-year CBC risk prediction estimated by the model. In this scenario, 55 CPM per 1,000 patients may be avoided using the model compared to counseling CPM to all patients with family history; see **Table S10** and **Figure S8**. The density distribution of the estimated 10-year CBC risk prediction was shown for patients with and without family history. The overlap between the two distributions reflects that a prediction model is useful to define high and low risk patients to counsel necessary CPM and avoid unnecessary surgeries in a setting where *BRCA1/2* mutations are not tested. The decision curves in **Figures S9 and S10** provide a comprehensive overview of the net benefit for a range of harm-benefit thresholds.

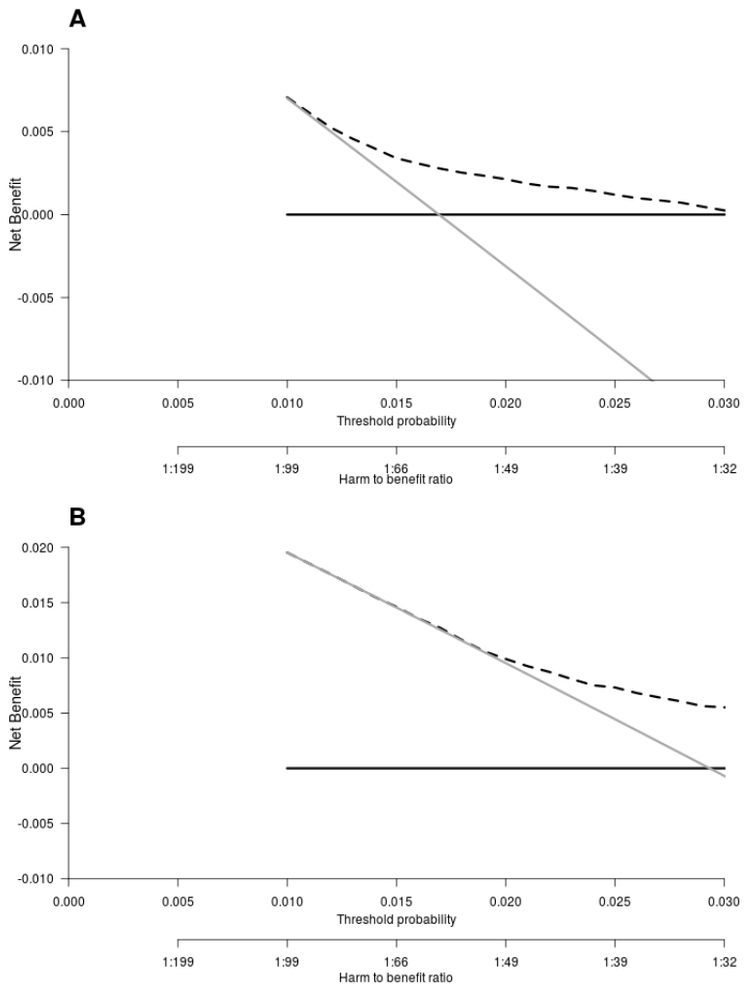

Figure S9: Decision curve analysis at 5 years for the contralateral breast cancer risk model without *BRCA* mutation information.
Panel A shows the decision curve to determine the net benefit of the estimated 5-year predicted contralateral breast cancer (CBC) cumulative incidence for patients without first-degree family history using the prediction model (dotted black line) compared to not treating any patients with contralateral preventive mastectomy (CPM) (black solid line). Panel B shows the decision curve to determine the net benefit of the estimated 5-year predicted CBC cumulative incidence for patients with first-degree family history of breast cancer using the prediction model (dotted black line) versus treating (or at least counseling) all patients (grey solid line). The y-axis measures net benefit, which is calculated by summing the benefits (true positives, i.e., patients with a CBC who needed a CPM) and subtracting the harms (false positives, i.e., patients with CPM who do not need it). The latter are weighted by a factor related to the relative harm of a non-prevented CBC versus an unnecessary CPM. The factor is derived from the threshold probability to develop a CBC at 5 years at which a patient would opt for CPM (e.g. 2.5%). The x-axis represents the threshold probability. Using a threshold probability of 2.5% implicitly means that CPM in 40 patients of whom one would develop a CBC if untreated is acceptable (39 unnecessary CPMs, harm to benefit ratio 1:39).

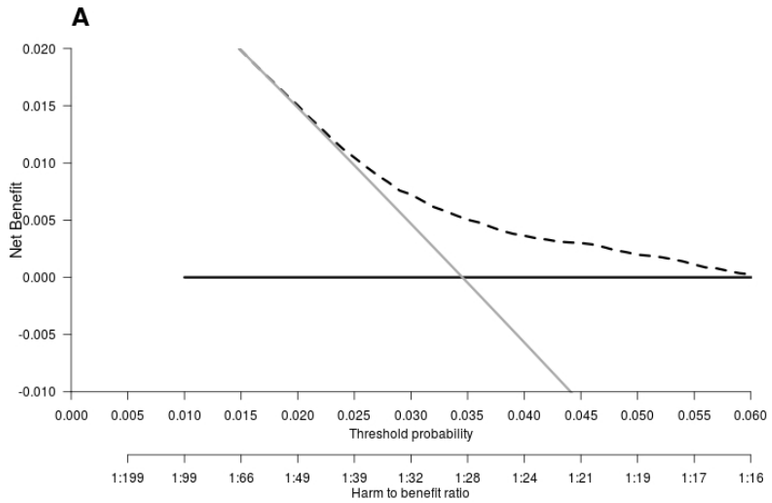

Figure S10: Decision curve analysis at 10 years for the contralateral breast cancer risk model without *BRCA* mutation information.
Panel A shows the decision curve to determine the net benefit of the estimated 10-year predicted contralateral breast cancer (CBC) cumulative incidence for patients without first-degree family history using the prediction model (dotted black line) compared to not treating any patients with contralateral preventive mastectomy (CPM) (black solid line). Panel B shows the decision curve to determine the net benefit of the estimated 10-year predicted CBC cumulative incidence for patients with first-degree family history using the prediction model (dotted black line) versus treating (or at least counseling) all patients (grey solid line). The y-axis measures net benefit, which is calculated by summing the benefits (true positives, i.e., patients with a CBC who needed a CPM) and subtracting the harms (false positives, i.e., patients with CPM who do not need it). The latter are weighted by a factor related to the relative harm of a non-prevented CBC versus an unnecessary CPM. The factor is derived from the threshold probability to develop a CBC at 10 years at which a patient would opt for CPM (e.g. 4.5%). The x-axis represents the threshold probability. Using a threshold probability of 4.5% implicitly means that CPM in 22 patients of whom one would develop a CBC if untreated is acceptable (21 unnecessary CPMs, harm to benefit ratio 1:21).

Table S10. Clinical utility of the 10-year contralateral breast cancer risk prediction model in non-*BRCA* tested patients. At the same probability threshold, the net benefit is exemplified in patients with family history (for avoiding unnecessary CPM) and patients without family history (performing necessary CPM).

		Family history		No family history	
Probability threshold p_t (%)	Unnecessary CPMs needed to prevent a CBC*	Net benefit versus treat all patients with CPM (per 1000)	Avoided unnecessary CPMs per 1000 patients	Net benefit versus treat none (per 1000)	Performed necessary CPMs per 1000 patients
3.5	27.6	0.3	8.3	5.0	137.9
4.5	21.2	2.6	55.2	3.0	63.7
5.5	17.2	8.2	140.9	1.1	18.9

CPM: contralateral mastectomy; CBC: contralateral breast cancer;
*The number of unnecessary contralateral preventive mastectomies needed to prevent a CBC is calculated by: $(1-p_t)/p_t$

9. Formula to estimate the contralateral breast cancer risk in patients not tested for BRCA

The formula for the alternative model is reported below. Baseline survival estimates according to the model and time are:

$$S_0(5) = 0.982$$
$$S_0(10) = 0.965$$

And
Linear Predictor (LP) =
+ 0.108 – 0.002 × Age – 0.018 × Age' + 0.473 × I[Family history = Yes] – 0.143 × I[Nodal status = positive] – 0.041 × I[Size of PBC = (2,5] *cm*] + 0.108 × I[Size of PBC = greater than 5 *cm*] + 0.181 × I[Morphology of PBC = lobular including mixed] – 0.032 × I[Grade of PBC = moderately differentiated] – 0.135 × I[Grade of PBC = poorly/undifferentiated]– 0.248 × I[Chemotherapy = yes] – 0.034 × I[Radiotherapy to the breast = yes] + 0.522 × I[ER-negative without endocrine therapy] + 0.592 × I[ER-positive without endocrine] + 0.232 × I[HER2-negative without trastuzumab] + 0.082 × I[HER2-positive without trastuzumab]

Where Age' = max(Age – 50, 0)

10. Assessment of limited information of contralateral preventive mastectomy (CPM)

Information about CPM was not available in most studies. This lack of information may underestimate the cumulative CBC incidence because patients underwent CPM should not be considered to be at risk to develop CBC, though a small proportion of 1.3% of CBC was observed after CPM among *BRCA1* or *BRCA2*-related breast cancer patients[20]. We

investigated the impact of CPM on CBC cumulative incidence estimation in the BOSOM and EMC datasets, in which this information was complete and CPM was not within 3 months after first BC diagnosis, i.e. for 3,760 out of 3,793 and 3,390 out of 3,398, respectively. In these two studies, we compared the estimated cumulative incidence curves in which we applied censoring for CPM or considering in the risk set patients experiencing CPM at first primary BC or during the follow-up.

Figure S11 shows the cumulative incidence estimation of the two scenarios. As expected, the cumulative incidence was underestimated when we ignored the occurrence of CPM. However, there was only a small difference between the two curves: the estimated cumulative incidence at 10 years was 5.6% (95% CI: 4.9 – 6.4%) considering CPM, and 5.3% (4.6 – 6.0%) not considering CPM in the BOSOM dataset; and 5.7% (5.0 – 6.6%) considering CPM, and 5.6% (4.8 – 6.4%) not considering CPM in the EMC dataset. Therefore, although the CPM was not available for most studies, we concluded that the cumulative incidence of CBC was only slightly underestimated due to missing CPM information.

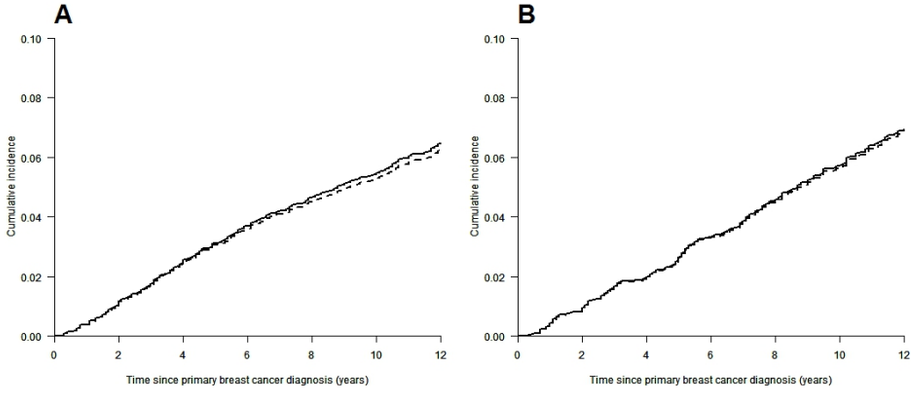

Figure S11: Assessment of inclusion of information of contralateral preventive mastectomy (CPM)**.** Panel A shows the contralateral breast cancer cumulative incidence curve in the BOSOM dataset. Panel B shows the contralateral breast cancer cumulative incidence curve in the EMC dataset. The bolded black lines indicate the estimated cumulative incidence curve censoring patients with CPM at first primary breast cancer or during the follow-up. The dotted lines indicate the estimated cumulative incidence curve considering patients with CPM still at risk during the follow-up.

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