Prediction of contralateral breast cancer: statistical aspects and prediction performance

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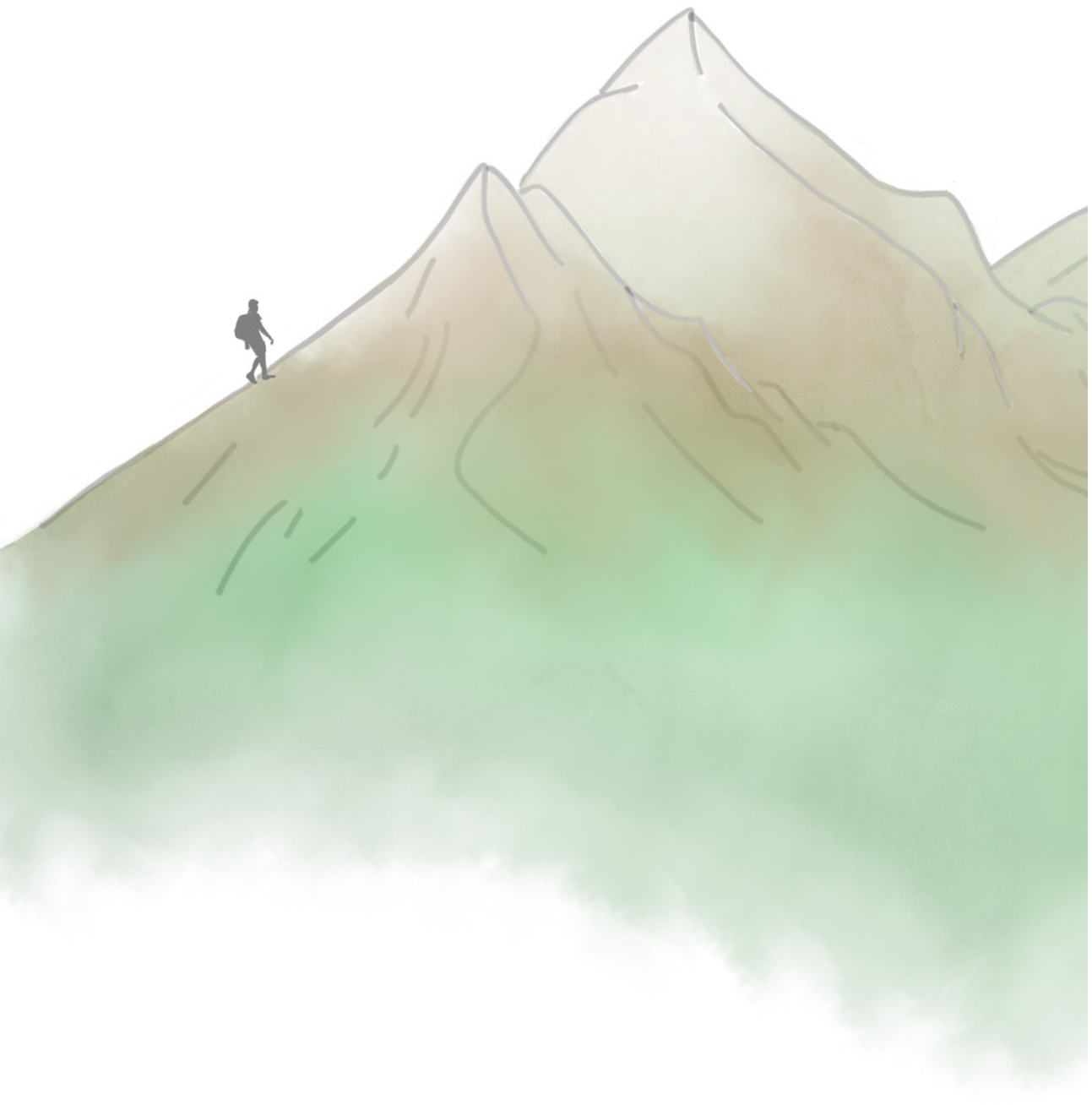

Chapter 4

PredictCBC-2.0: a contralateral breast cancer risk prediction model developed and validated in ~200,000 patients

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ABSTRACT

Background

Prediction of contralateral breast cancer (CBC) risk is challenging due to moderate performances of the known risk factors. We aimed to improve our previous risk prediction model (PredictCBC) by updated follow-up and including additional risk factors.

Methods

We included data from 207,510 invasive breast cancer patients participating in 23 studies. 8,225 CBC events occurred over a median follow-up of 10.2 years. In addition to the previously included risk factors, PredictCBC-2.0 included *CHEK2* c.1100delC, a 313 variant polygenic risk score (PRS-313), body mass index (BMI), and parity. Fine and Gray regression was used to fit the model. Calibration and a time-dependent Area Under the Curve (AUC) at 5 and 10 years were assessed to determine the performance of the models. Decision curve analysis was performed to evaluate the net benefit of PredictCBC-2.0 and previous PredictCBC models.

Results

The discrimination of PredictCBC-2.0 at 10 years was higher than PredictCBC with an AUC of 0.65 (95% prediction intervals (PI):0.56–0.74) versus 0.63 (95%PI:0.54–0.71). PredictCBC-2.0 was well-calibrated with an observed/expected (O/E) ratio at 10 years of 0.92 (95%PI:0.34–2.54). Decision curve analysis for contralateral preventive mastectomy (CPM) showed potential clinical utility of PredictCBC-2.0 between thresholds of 4–12% 10-year CBC risk for *BRCA1/2* mutation carriers and non-carriers.

Conclusions

Additional genetic information beyond *BRCA1/2* germline mutations improved CBC risk prediction and might help tailor clinical decision making towards CPM or alternative preventive strategies. Identifying patients who benefit from CPM, especially in the general breast cancer population, remains challenging.

INTRODUCTION

Contralateral breast cancer (CBC) is the most common second primary cancer among women diagnosed with first primary invasive breast cancer (BC)[1]. CBC accounts for approximately 40-50% of all new secondary cancers in women with first primary invasive BC and has potentially less favorable prognosis[2-6]. Worries regarding CBC risk have increased the demand for contralateral preventive mastectomy (CPM)[7, 8]. However, the impact of CPM on survival is uncertain, especially in women with low risk to develop a CBC[9-13].Thus, improved CBC risk prediction is important in order to inform decision making on surveillance and preventive strategies. Currently, the most important factor for decision making on CPM is the *BRCA1/2* mutations status[14].

We previously developed and cross-validated two models using data from 132,756 invasive BC patients with a median follow-up of 8.8 years including 4,672 CBC events[15]. One model (PredictCBC-1A) was developed including information about *BRCA1/2* mutation status and another (PredictCBC-1B) for the general breast cancer population of genetically untested women. Two other specific CBC prediction tools are currently available in the literature: the Manchester formula (part of the Manchester guidelines for CPM) and CBCrisk[15-18].

In addition to *BRCA1/2* mutations, other genetic risk factors for breast cancer are also associated with CBC risk. In particular, there is substantial evidence that the *CHEK2* c.1100delC variant increases the risk of developing CBC[19, 20]. In addition, polygenic risk scores (PRS) of common variants, developed for association with a first breast cancer have been shown to predict CBC in the general BC population and in *BRCA1/2* mutation carriers[21-24], particularly the extensively validated 313 SNP PRS[25]. With regard to the lifestyle and reproductive factors, there is evidence that body mass index (BMI) and parity at or around the time of the first primary invasive BC diagnosis are associated with CBC risk[26].

Our aim was to refit PredictCBC models incorporating these additional risk factors. We utilized the same dataset but with updated follow-up, and added additional studies, especially one large study of *BRCA1* and *BRCA2* mutation carriers. We evaluated the potential improvement in prediction performance and utility for clinical decision making of the updated models for both *BRCA1/2* carriers as the general (non-tested) breast cancer population (PredictCBC-2.0).

MATERIAL AND METHODS

Study population and available data

We used the data from the same five main sources previously used to develop PredictCBC models to develop the PredictCBC-2.0 models including updated follow-up information, additional patients and CBC events[15]. Two studies were addionally included from the Breast Cancer Association Consortium (BCAC) compared to the version of the BCAC data used to develop PredictCBC-1A and PredictCBC-1B models. Most of the studies were either population- or hospital-based series; and most women were of European-descent (**Supplementary Tables 1-2,** available online). We also additionally included patients selected from the Hereditary Breast and Ovarian cancer study in the Netherlands (HEBON)[27], a nationwide study based on clinical genetic centers. The eligibility criteria were the same as previously: briefly, we included female patients with invasive first primary BC with no sign of distant metastases at diagnosis or prior history of cancer (except for non-melanoma skin cancer)[15]. We included women diagnosed after 1990 so that diagnostic and treatment procedures were close to modern practice while follow-up was sufficient to study CBC incidence. In total 207,510 women from 23 studies were included. All studies were approved by the appropriate ethics and scientific review boards. All women provided written informed consent; or, for some Dutch cohorts as applicable, the secondary use of clinical data was in accordance with Dutch legislation and codes of conduct[28, 29]. Information on the factors included in the analyses, follow-up per dataset, and study design are in **Supplementary Table 2,** available online.

Statistical analyses

Primary endpoint and follow-up

The primary endpoint in the analyses was incidence of invasive or in situ metachronous CBC. Follow-up started 3 months after invasive first primary BC diagnosis, to exclude synchronous CBCs, and ended at date of CBC, distant metastasis (but not a loco-regional relapse), CPM, or last date of follow-up (due to death, loss to follow-up, or end of study), whichever occurred first. For 36,553 (17.6%) women, from BCAC and HEBON, recruitment or blood sampling for DNA testing occurred more than 3 months after diagnosis of the first primary BC. For these women, follow-up (prevalent cases), started at recruitment or at the date of blood draw or at DNA test result (left truncation). Patients who underwent CPM during the follow-up were censored because of negligible CBC risk after a CPM[30]. Missing data were multiply imputed by chained equations (MICE) to avoid loss of information due to case-wise deletion[31-33](**Supplementary Material**, available online).

Model development and validation

We used multivariable Fine and Gray regression models to account for death and distant metastases as competing events[34]. Analyses were stratified by study to allow baseline hazard (sub)distributions to differ across studies. The assumption of proportional subdistribution hazards was graphically checked using Schoenfeld residuals[35]. The resulting subdistribution hazard ratios (sHRs) and corresponding 95% confidence intervals (CI) were pooled from 5 imputed data sets using Rubin's rules[33]. We re-estimated the coefficients of PredictCBC-1A and PredictCBC-1B, and we re-fitted the PredictCBC models using the extended data set with updated follow-up time. PredictCBC-1A, developed including information about *BRCA1/2* mutation carrier status, was extended by including *CHEK2* c.1110delC status, PRS-313, BMI, and parity (hereafter: PredictCBC-2.0A)[15]. *CHEK2* c.1110delC and PRS-313 were derived from the BCAC database, as published previously[25, 36, 37]. We extended PredictCBC-1B, developed for genetically untested women, incorporating BMI and parity (hereafter: PredictCBC-2.0B). Potential non-linear relations between continuous predictors and CBC risk were investigated using restricted cubic splines with three knots.

The validity of the model was investigated by leave-one-study-out cross-validation[38]. In each validation cycle, all studies were analyzed except one, in which the validity of the model was evaluated. Since some BCAC studies had insufficient CBC events required for reliable validation, we used the geographic area as unit for splitting[38-40]. Nineteen out of 23 studies were combined in 4 geographic areas. (**Supplementary Table 3**, available online). A total of 8 units of splitting including 4 geographic ares and 4 studies were used to cross-validated the models.

The performance of the PredictCBC-2.0 was assessed by discrimination, i.e., the ability to differentiate between patients diagnosed with CBC and those who were not, and by calibration, which measures the agreement between the actual (observed) risk and CBC risk estimated by the prediction models (predicted). Discrimination was quantified by time-dependent areas under the ROC curve (AUCs) based on Inverse Censoring Probability Weighting at 5 and 10 years[41]. Values of AUCs close to 1 indicate good discrimination, while values close to 0.5 indicated poor discrimination. Calibration was assessed by the observed to expected (O/E) ratio and calibration plots at 5 and 10 years[42, 43]. An O/E ratio lower or higher than 1 indicates that average predictions are too high or low, respectively.

To consider heterogeneity among studies, a random-effect meta-analysis was performed to provide summaries of discrimination and calibration performance. The 95% prediction intervals (PI) indicate the likely performance of the model in a new dataset. The summary performances of PredictCBC-2.0 and 1.0 models were compared to evaluate whether adding the new predictors improved the performance of CBC risk prediction. We developed and validated the risk prediction model following the

Transparent Reporting of a Multivariable Prediction model for Individual Prognosis or Diagnosis (TRIPOD)statement[44]. Analyses were done in SAS (SAS Institute Inc., Cary, NC, USA) and R (version 3.6.1).

Clinical utility

The clinical utility of the prediction models was evaluated using decision curve analysis (DCA)[45, 46]. A key metric DCA is the net benefit, which is the number of true-positive classifications (in this example: the number of CPMs in patients who would have developed a CBC) minus the weighted number of false-positive classifications (in this example: the number of unnecessary CPMs in patients 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 fixed time horizon (e.g., CBC risk at 5 or 10 years) [47]. 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 considered among *BRCA1/2* mutation carriers, the decision curve analysis was reported among *BRCA1/2* mutation carriers and non-carriers separately[48]. Among patients not tested for *BRCA1/2* germline mutations, we assumed that the decision for CPM is based on family history of breast cancer. Net benefits of PredictCBC-2.0A and PredictCBC-2.0B were compared with net benefit of PredictCBC-1A and 1B, respectively, to assess the potential improvement in clinical utility of the updated models.

RESULTS

A total of 207,510 women with invasive first primary BC diagnosed between 1990 and 2017, with 8,225 CBC events (6,828 invasive, 1,397 in situ), from 23 studies, were used for prediction modeling for CBC risk (**Supplementary Table 2**, available online). Median follow-up time was 10.2 years and CBC cumulative incidences at 5 and 10 years were 2.2% and 4.1%, respectively. Details of the studies and patient, tumor, and treatment characteristics are provided in **Supplementary Table 4** (available online). The multivariable models with estimates for all included factors are shown in **Table 1**.

Most of factors were independently associated with CBC risk, including the new factors incorporated in the PredictCBC-2.0 models, i.e., s BMI, parity, *CHEK2* c.1110delC, and PRS-313. There was no evidence against log-linear relationships between BMI, parity and PRS-313 and CBC risk. Non-linearity between age at first BC diagnosis and CBC risk was accounted for with a linear spline at age 60 years. The formulae of the PredictCBC models are provided in **Supplementary Methods** (available online). To calculate the predicted CBC cumulative incidence, we used the event-free baseline probability of the Netherlands Cancer Registry (NCR), as previously[15].

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

Factor (reference)		PredictCBC-2.0A	PredictCBC-2.0B
		sHR (95% CI)	sHR (95% CI)
Age at PBC, *years* (75th vs 25th quartile: 66 vs 48)		0.87[a] (0.83 - 0.90)	0.82[a] (0.78 - 0.85)
Body mass index, *kg/m*^{2} (75th vs 25th quartile: 28.4 vs 22.7)		1.06 (1.03 - 1.09)	1.06 (1.03 - 1.09)
Parity (75th vs 25th quartile: 3 vs 1)		0.85 (0.82 - 0.88)	0.86 (0.83 - 0.90)
Family history (yes)		1.17 (1.12 - 1.23)	1.35 (1.29 - 1.42)
BRCA mutation			
	BRCA1 vs non-carrier	4.79 (4.43 - 5.17)	-
	BRCA2 vs non-carrier	3.09 (2.72 - 4.25)	-
PRS_{313}[b] (75th vs 25th quartile: -0.49 vs 0.32)		1.35 (1.31 - 1.39)	-
CHEK2 c.1100delC mutation (present)		2.75 (2.85 - 3.34)	-
Nodal status of FBC (positive)		0.99 (0.93 - 1.05)	0.99 (0.93 - 1.04)
Tumor size category of FBC, *cm*			
	(2,5] vs ≤ 2	0.99 (0.94 - 1.05)	1.01 (0.96 - 1.07)
	> 5 vs ≤ 2	1.23 (1.10 - 1.36)	1.22 (1.09 - 1.36)
Morphology of FBC (lobular including mixed)		1.19 (1.12 - 1.27)	1.17 (1.10 - 1.24)
Grade of FBC			
	Moderately differentiated vs well differentiated (II vs I)	0.93 (0.88 - 0.99)	0.98 (0.93 - 1.04)
	Poorly differentiated vs well differentiated (III vs I)	0.85 (0.79 - 0.91)	0.95 (0.88 - 1.01)
Chemotherapy (yes)		0.75 (0.70 - 0.80)	0.75 (0.70 - 0.80)
Radiotherapy to the breast (yes)		0.93 (0.89 - 0.98)	0.95 (0.90 - 0.99)
ER with endocrine therapy			
	negative/no vs positive/yes	1.53 (1.43 - 1.65)	1.78 (1.67 - 1.90)
	positive/no vs positive/yes	1.95 (1.83 - 2.07)	1.94 (1.82 - 2.06)
HER2 with trastuzumab therapy			
	negative/no vs positive/yes	1.22 (1.09 - 1.38)	1.30 (1.15 - 1.46)
	positive/no vs positive/yes	1.12 (0.97 - 1.28)	1.14 (1.00 - 1.31)

Abbreviations:
vs: versus; sHR: subdistributional hazard ratio; CI: confidence interval; PRS: polygenic risk score; PBC: first primary breast cancer; ER: estrogen receptor; HER2: human epidermal growth factor 2;
[a] age was parametrized as a linear spline with one interior knot at 60 years. For representation purposes, we here provide the sHR for the 75th versus the 25th percentile.
[b] PRS standardized by the same standard deviation (SD) used by Mavaddat et al (SD=0.61)[25].

The AUCs at 5 and 10 years of PredictCBC-2.0A were higher than of PredictCBC-1A at 5 years: 0.66, 95% prediction interval (PI): 0.55–0.76 versus 0.62 (95%PI:0.51–0.74); and at 10 years: 0.65 (95%PI:0.56–0.74) versus 0.63 (95%PI:0.54–0.71)(**Figure 1-2, Table 2**). The AUCs for PredictCBC-2.0B and PredictCBC-1B were both 0.59 (95%PI: PredictCBC-2.0B:0.51–0.68; PredictCBC-1B:0.49–0.69) at 5 years and both 0.58 (95%PI:0.51–0.65) at 10 years (**Figure 1-2, Table 2**).

The O/E ratio at 5 and 10 years across all versions of PredictCBC models ranged between 0.90 and 0.92 with similar 95%PIs (**Figure 1-2, Table 2**). Calibration plots of PredictCBC 2.0 models are provided in the **Supplementary Figures 1-4** (available online).

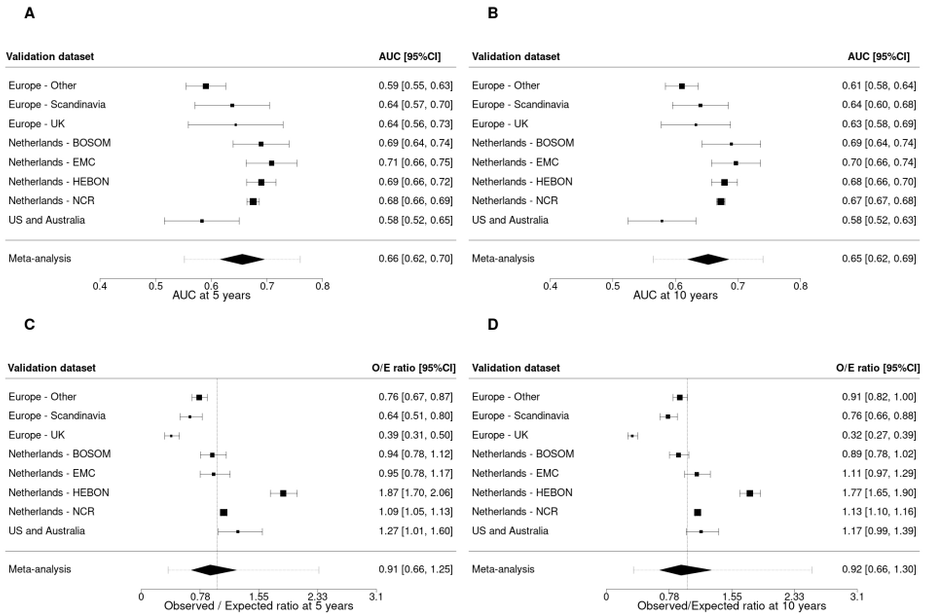

Figure 1. Analysis of predictive performance of PredictCBC-2.0A in leave-one-study-out cross-validation. Discrimination was assessed by a time-dependent AUC at 5 and 10 years (panel A and B, respectively). Calibration accuracy was measured with observed/expected (O/E) ratio at 5 and 10 years (panel C and D, respectively). 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.

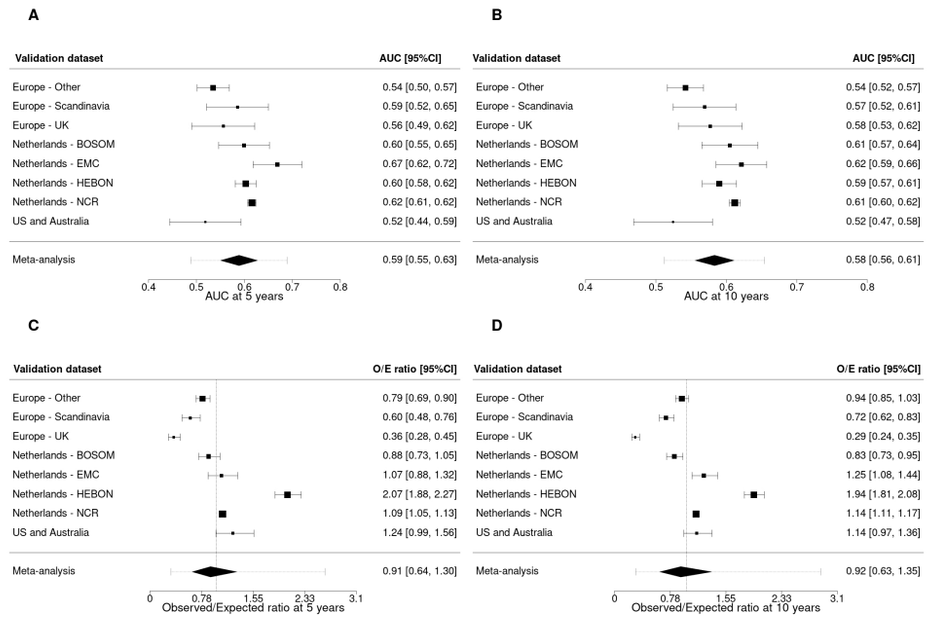

Figure 2. Analysis of predictive performance of PredictCBC-2.0B in leave-one-study-out cross-validation. Discrimination was assessed by a time-dependent AUC at 5 and 10 years (panel A and B, respectively). Calibration accuracy was measured with observed/expected (O/E) ratio at 5 and 10 years (panel C and D, respectively). 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.

Table 2. Summary of prediction performance of PredictCBC-1A, PredictCBC-1B, PredictCBC-2.0A and PredictCBC-2.0B with the corresponding 95% prediction intervals (PI) based on a leave-one-study out cross-validation procedure.

CBC risk prediction model	Performance measure			
	Discrimination		Calibration	
	AUC (95% PI)		O/E ratio (95% PI)	
	5-year	10-year	5-year	10-year
PredictCBC-1A	0.62 (0.51-0.74)	0.63 (0.54-0.71)	0.90 (0.36-2.24)	0.91 (0.34-2.48)
PredictCBC-2.0A	0.66 (0.55-0.76)	0.65 (0.56-0.74)	0.91 (0.35-2.34)	0.92 (0.34-2.54)
PredictCBC-1B	0.59 (0.49-0.69)	0.58 (0.51-0.65)	0.91 (0.32-2.55)	0.92 (0.30-2.80)
PredictCBC-2.0B	0.59 (0.51-0.68)	0.58 (0.51-0.65)	0.91 (0.31-2.63)	0.92 (0.30-2.87)

Abbreviations: AUC: Area under the Curve; CBC: contralateral breast cancer; PI: prediction interval; O/E = observed/expected

The decision curves showed the net benefit for a range of harm-benefit thresholds at 10-year CBC risk (**Figure 4**). We evalutated the potential clinical utility of PredictCBC-2A versus PredictCBC-1.0A for decision thresholds between 4-12% for the 10-year CBC risk among *BRCA1/2* mutation carriers and non-carriers (**Table 3**). For example, if consensus guidelines would indicate acceptability of one in 10 patients for whom a CPM is recommended developing 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 models. Compared with a strategy recommending CPM to all *BRCA1*/2 mutation carriers, PredictCBC-1A avoids 76.9 net CPMs per 1,000 patients (**Table 3**). An additional 50.0 CPMs may be avoided using PredictCBC-2.0A compared to PredictCBC-1A. In contrast, almost no non-*BRCA1/2* mutation carriers had predictions above the 10% threshold (general BC population, **Table 3**); three necessary CPMs per 1,000 patients would be indicated using PredictCBC-2.0A. Analyses for PredictCBC-1B and PredictCBC-2.0B at 10 years suggested a potential clinical utility between 4-6% 10-year CBC risk for patients with and without family history (**Table 3 and Figure 4)**. No remarkable improvement in net benefit was detected using PredictCBC-2.0B compared to PredictCBC-1B in decision making regarding CPM (**Table 3 and Figure 4)**. Decision curves for CBC risk using PredictCBC and PredictCBC-2.0 at 5 years and the corresponding clinical utility showed similar patterns (**Supplementary Figures S5-6** and **Supplementary Table 5**, available online).

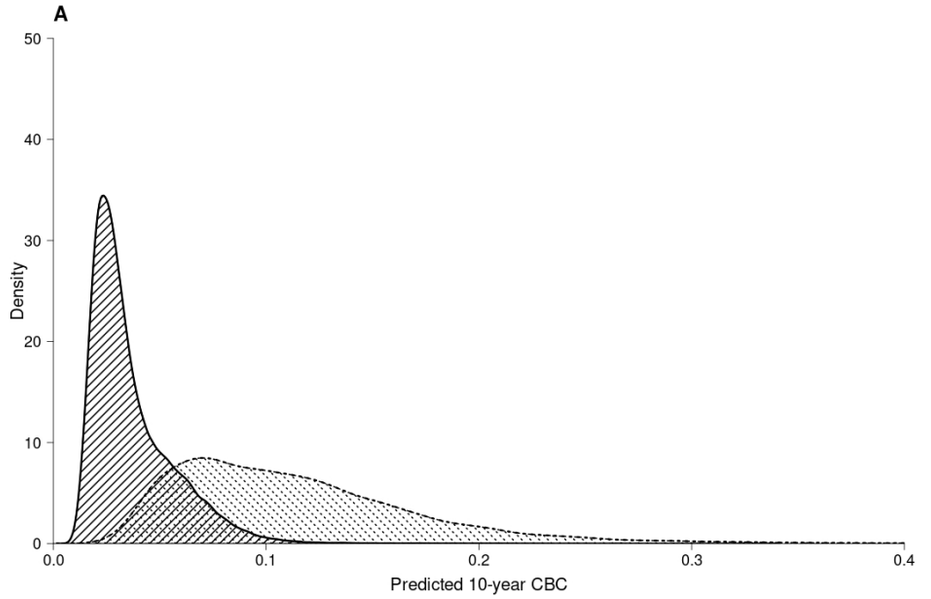

Figure 3. Density distribution of 10-year predicted contralateral breast cancer using PredictCBC version 2 models. **a** Density distribution of 10-year predicted contralateral breast cancer absolute risk using PredictCBC-2.0A within non-carriers (area with black solid lines) and *BRCA1/2* mutation carriers (area with black dashed lines). **b** Density distribution of 10-year predicted contralateral breast cancer absolute risk using PredictCBC-2.0B within patients without (first degree) family history (area with black solid lines) and patients with (first degree) family history (area with black dashed lines).

Table 3: Clinical utility of the 10-year contralateral breast cancer risk prediction models (PredictCBC-1A with PredictCBC-2.0A and PredictCBC-1B with PredictCBC-2.0B). For PredictCBC versions 1A and 2.0A, 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). For PredictCBC versions 1B and 2.0B, 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).

PredictCBC-1A and PredictCBC-2.0A							
		BRCA1/2 mutation carriers			Non-carriers		
Probability threshold p_t (%)	Unnecessary CPMs needed to detect one necessary CPM*	Net benefit versus treat all patients with CPM (per 1000)	Avoided unnecessary CPMs per 1000 patients using PredictCBC-1A	Additional avoided unnecessary CPMs per 1000 patients using PredictCBC-2.0A	Net benefit versus treat none (per 1000)	Performed necessary CPMs per 1000 patients using PredictCBC-1A	Additional performed necessary CPMs per 1000 patients using PredictCBC-2.0A
4	24	0.1	0.3	1.9	4.8	115.7	15.3
6	15.7	No benefit	0.0	20.0	0.6	9.3	22.9
8	11.5	3.5	40.6	52.0	No benefit	0.0	9.0
10	9.0	8.5	76.9	50.2	No benefit	0.0	3.4
12	7.3	22.4	164.0	15.0	No benefit	0.0	1.1
PredictCBC-1B and PredictCBC-2.0B							
		Family history			No family history		
Probability threshold p_t (%)	Unnecessary CPMs needed to detect one necessary CPM*	Net benefit versus treat all patients with CPM (per 1000)	Avoided unnecessary CPMs per 1000 patients using PredictCBC-1B	Additional avoided unnecessary CPMs per 1000 patients using PredictCBC-2.0B	Net benefit versus treat none (per 1000)	Performed necessary CPMs per 1000 patients using PredictCBC-1B	Additional performed necessary CPMs per 1000 patients using PredictCBC-2.0B
4	24	3.4	80.8	5.9	5.4	130.4	0.0
5	19	9.4	177.9	0.0	2.4	46.5	0.1
6	15.7	15.9	248.7	4.0	0.5	7.1	7.5

CPM: contralateral preventive mastectomy;
* The number of unnecessary contralateral mastectomies needed to detect one necessary CPM is calculated by: (1-pt)/pt

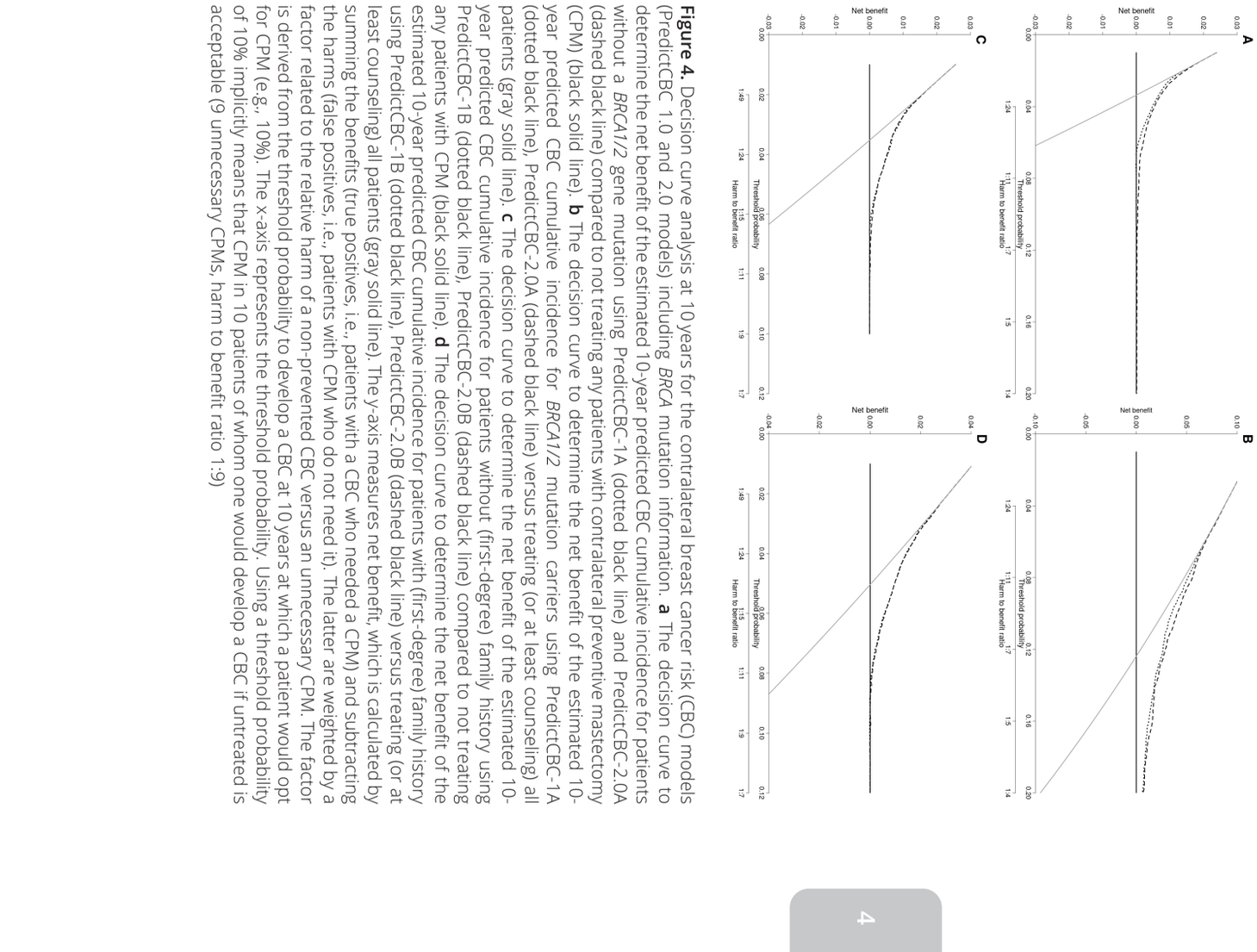

Figure 4. Decision curve analysis at 10 years for the contralateral breast cancer risk (CBC) models (PredictCBC 1.0 and 2.0 models) including *BRCA* mutation information. **a** The decision curve to determine the net benefit of the estimated 10-year predicted CBC cumulative incidence for patients without a *BRCA1/2* gene mutation using PredictCBC-1A (dotted black line) and PredictCBC-2.0A (dashed black line) compared to not treating any patients with contralateral preventive mastectomy (CPM) (black solid line). **b** The decision curve to determine the net benefit of the estimated 10-year predicted CBC cumulative incidence for *BRCA1/2* mutation carriers using PredictCBC-1A (dotted black line), PredictCBC-2.0A (dashed black line) versus treating (or at least counseling) all patients (gray solid line). **c** The decision curve to determine the net benefit of the estimated 10-year predicted CBC cumulative incidence for patients without (first-degree) family history using PredictCBC-1B (dotted black line), PredictCBC-2.0B (dashed black line) compared to not treating any patients with CPM (black solid line). **d** 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 PredictCBC-1B (dotted black line), PredictCBC-2.0B (dashed black line) versus treating (or at least counseling) all patients (gray solid line). The y-axis measures net benefit, which is calculated by summing the benefits (true 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)

DISCUSSION

We evaluated the potential improvement of CBC risk prediction by adding established genetic (*CHEK2* c.1100delC and PRS-313) and life-style (BMI and parity) factors to the previous PredictCBC models, and used additional follow-up information and new studies to provide more reliable estimates.

The current clinical recommendations of CPM are mostly based on the presence of a pathogenic mutation in *BRCA1/2*[49, 50]. This seems a reasonable approach according to CBC risk predictions based on the PredictCBC models: few non-*BRCA1/2* carriers exceed a 10% 10-year risk threshold. However, approximately 40% of *BRCA1/2* mutation carriers do not reach this threshold either, suggesting that a significant proportion of *BRCA1/2* carriers might be spared CPM. Additional genetic information beyond *BRCA1/2* germline mutation such as the presence of the *CHEK2* c.1110delC variant and PRS-313 might improve decision making.

Currently available CBC models, such as CBCrisk and the Manchester formula, show only moderate discrimination[51]. In addition, the Manchester formula has been shown to systematically overestimate CBC risk[51]. The BOADICEA model, a well-known risk prediction tool to estimate risk of developing first primary BC, also allows the calculation of CBC risk[52-55]. Although BOADICEA includes rare pathogenic variants in moderate and high risk BC susceptibility genes (i.e., *BRCA1*, *BRCA2*, *PALB2*, *ATM* and *CHEK2*, *BARD1*, *RAD51C*, *RAD51D*), and PRS-313, it does not incorporate information on systemic treatment of the primary BC, which are important predictors of CBC risk[56].

A model for prediction of recurrence, the INFLUENCE nomogram, was developed to estimate five-year recurrence risk as well as conditional annual risks of developing a local or regional recurrence based on first BC and treatment characteristics[57]. A more recent version (INFLUENCE 2.0) also provides 5-year individualized predictions for secondary primary breast cancer based on cases older than 50 years at first cancer diagnosis from the NCR nationwide cohort irrespective of their genetic status or testing status using random survival forests[58]. The model provided moderate discrimination (AUC at 5 years: 0.67; 95%CI:0.65–0.68) using internal validation. In our comparable population- and hospital-based Dutch series, EMC and NCR, the AUCs at 5 years of PredictCBC-1A were 0.69 (95%CI:0.64–0.73) and 0.66 (95%CI:0.65–0.67), and of PredictCBC-2.0A 0.71 (95%CI:0.66–0.75) and 0.68 (95%CI:0.66–0.69), respectively. Moreover, INFLUENCE 2.0 is only relevant for the general population, while PredictCBC can also be used in the clinical genetic setting. Notably, we demonstrated that decision making about preventive strategies in clinical practice is unlikely to improve without genetic information.

Our work has some limitations: firstly, 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 NCR population, as described previously[15]. 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 9%. Secondly, important predictors such as family history, *BRCA1/2* and *CHEK2* c.1110delC status, and PRS-313, were only available in a subset of the women, although the multiple imputation approach should lead to consistent estimates[59-61]. Detailed information about family history would have been useful to improve CBC risk prediction, especially among patients with a mutation in *BRCA1/2* or *CHEK2*. Nonetheless, we considerably increased the number of patients with *BRCA1/2* mutation status and family history information compared to our previous publication (40,343 vs 7,704 and 53,399 vs 30,541 patients with available *BRCA* mutation status and family history information, respectively), and added *CHEK2* c.1110delC, which is a founder mutation present in approximately 0.5–1.6% of individuals of Northern and Eastern European descent and explains the large majority of carriers of *CHEK2* protein truncating variants in these populations[19, 62]. Further validation will be required to investigate how well PredictCBC models predict risk in other populations. In particular, the model was developed in patients of European ancestry and further evaluation and adaptation will be needed to extend PredictCBC models to non-European populations[63, 64]. Future research might also include comparisons of machine learning (ML) methods with classical statistical regression models[65, 66].

The prediction models may be further improved by including additional risk factors. In particular, rare mutations in other breast cancer susceptibility genes, such as *ATM* and *PALB2* are also likely to be associated with an increased risk of CBC[22, 67, 68]. The discrimination provided by the PRS will also improve as more SNPs are added[69, 70]. Prediction performance might also be improved by adding breast density and other risk factors, modelled dynamically in a time dependent fashion[71]. Finally, we wish to emphasize that adequate presentation (e.g., with online tools) of the risk estimates is crucial for effective communication about CBC risk during doctor-patient consultations[72, 73].

CONCLUSIONS

In conclusion, we present an updated version of a previously proposed contralateral breast cancer risk model (PredictCBC) including additional information on breast cancer genetic variants beyond *BRCA1/2*, lifestyle and reproductive factors. PredictCBC-2.0, available online, is based on longer follow-up from a wide range of new European-descent population and hospital-based studies, with satisfactory calibration. PredictCBC

2.0 may be used to tailor clinical decision making towards CPM or alternative preventive strategies, especially when genetic information is available.

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; **ICPW:** Inverse censoring probability weighting; **MICE:** Multiple imputation by chained equations; **PI:** Prediction interval; **PR:** Progesterone receptor; **SEER:** Surveillance, Epidemiology and End Results; **TNM:**TNM Classification of Malignant Tumors.

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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. Pseudomised data sets that were used in the analyses can be requested from the Netherlands Cancer Registry, the Netherlands Cancer Institute, ErasmusMC, and the Breast Cancer Assocation Consortium.

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Authors' contributions

MKS, 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. All remaining authors contributed to critical revision and editing of the final version of the manuscript for publication. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Each study was approved by its institutional ethical review board.

Data availability statement

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 an anonymized form via the corresponding author on reasonable request and after approval of the involved institutions

Competing interests

The authors declare that they have no competing interests.

REFERENCES

1. Chen Y, Thompson W, Semenciw R, *et al.* Epidemiology of contralateral breast cancer. Cancer Epidemiol Biomarkers Prev 1999;8(10):855-61.
2. Gao X, Fisher SG, Emami B. Risk of second primary cancer in the contralateral breast in women treated for early-stage breast cancer: a population-based study. Int J Radiat Oncol Biol Phys 2003;56(4):1038-45.
3. Curtis RE, Ron E, Hankey BF, *et al.* New Malignancies Following Breast Cancer. In. *New malignancies among cancer survivors: SEER Cancer Registries, 1973-2000*, 181-205.
4. Yu GP, Schantz SP, Neugut AI, *et al.* Incidences and trends of second cancers in female breast cancer patients: a fixed inception cohort-based analysis (United States). Cancer Causes Control 2006;17(4):411-20.
5. Soerjomataram I, Louwman WJ, Lemmens VE, *et al.* Risks of second primary breast and urogenital cancer following female breast cancer in the south of The Netherlands, 1972-2001. Eur J Cancer 2005;41(15):2331-7.
6. Schaapveld M, Visser O, Louwman WJ, *et al.* The impact of adjuvant therapy on contralateral breast cancer risk and the prognostic significance of contralateral breast cancer: a population based study in the Netherlands. Breast Cancer Res Treat 2008;110(1):189-97.
7. Tuttle TM, Habermann EB, Grund EH, *et al.* Increasing use of contralateral prophylactic mastectomy for breast cancer patients: a trend toward more aggressive surgical treatment. J Clin Oncol 2007;25(33):5203-9.
8. Narod SA. Bilateral breast cancers. Nat Rev Clin Oncol 2014;11(3):157-66.
9. Metcalfe K, Gershman S, Ghadirian P, *et al.* Contralateral mastectomy and survival after breast cancer in carriers of BRCA1 and BRCA2 mutations: retrospective analysis. BMJ 2014;348:g226.
10. Xiong Z, Yang L, Deng G, *et al.* Patterns of Occurrence and Outcomes of Contralateral Breast Cancer: Analysis of SEER Data. J Clin Med 2018;7(6).
11. Wong SM, Freedman RA, Sagara Y, *et al.* Growing Use of Contralateral Prophylactic Mastectomy Despite no Improvement in Long-term Survival for Invasive Breast Cancer. Ann Surg 2017;265(3):581-589.
12. Murphy JA, Milner TD, O'Donoghue JM. Contralateral risk-reducing mastectomy in sporadic breast cancer. Lancet Oncol 2013;14(7):e262-9.
13. Basu NN, Hodson J, Chatterjee S, *et al.* The Angelina Jolie effect: Contralateral risk-reducing mastectomy trends in patients at increased risk of breast cancer. Sci Rep 2021;11(1):2847.
14. Domchek SM. Risk-Reducing Mastectomy in BRCA1 and BRCA2 Mutation Carriers: A Complex Discussion. JAMA 2019;321(1):27.
15. Giardiello D, Steyerberg EW, Hauptmann M, *et al.* Prediction and clinical utility of a contralateral breast cancer risk model. Breast Cancer Res 2019;21(1):144.
16. Basu NN, Ross GL, Evans DG, *et al.* The Manchester guidelines for contralateral risk-reducing mastectomy. World J Surg Oncol 2015;13:237.
17. Chowdhury M, Euhus D, Onega T, *et al.* A model for individualized risk prediction of contralateral breast cancer. Breast Cancer Res Treat 2017;161(1):153-160.
18. Chowdhury M, Euhus D, Arun B, *et al.* Validation of a personalized risk prediction model for contralateral breast cancer. Breast Cancer Res Treat 2018;170(2):415-423.
19. Weischer M, Nordestgaard BG, Pharoah P, *et al.* CHEK2*1100delC heterozygosity in women with breast cancer associated with early death, breast cancer-specific death, and increased risk of a second breast cancer. J Clin Oncol 2012;30(35):4308-16.
20. Akdeniz D, Schmidt MK, Seynaeve CM, *et al.* Risk factors for metachronous contralateral breast cancer: A systematic review and meta-analysis. Breast 2019;44:1-14.
21. Robson ME, Reiner AS, Brooks JD, *et al.* Association of Common Genetic Variants With Contralateral Breast Cancer Risk in the WECARE Study. J Natl Cancer Inst 2017;109(10).
22. Fanale D, Incorvaia L, Filorizzo C, *et al.* Detection of Germline Mutations in a Cohort of 139 Patients with Bilateral Breast Cancer by Multi-Gene Panel Testing: Impact of Pathogenic Variants in Other Genes beyond BRCA1/2. Cancers (Basel) 2020;12(9).
23. Kramer I, Hooning MJ, Mavaddat N, *et al.* Breast Cancer Polygenic Risk Score and Contralateral Breast Cancer Risk. Am J Hum Genet 2020;107(5):837-848.
24. Lakeman IMM, van den Broek AJ, Vos JAM, *et al.* The predictive ability of the 313 variant-based polygenic risk score for contralateral breast cancer risk prediction in women of European ancestry with a heterozygous BRCA1 or BRCA2 pathogenic variant. Genet Med 2021; 10.1038/s41436-021-01198-7.
25. Mavaddat N, Michailidou K, Dennis J, *et al.* Polygenic Risk Scores for Prediction of Breast Cancer and Breast Cancer Subtypes. Am J Hum Genet 2019;104(1):21-34.
26. Akdeniz D, Klaver MM, Smith CZA, *et al.* The impact of lifestyle and reproductive factors on the risk of a second new primary cancer in the contralateral breast: a systematic review and meta-analysis. Cancer Causes Control 2020;31(5):403-416.
27. Pijpe A, Manders P, Brohet RM, *et al.* Physical activity and the risk of breast cancer in BRCA1/2 mutation carriers. Breast Cancer Res Treat 2010;120(1):235-44.
28. Riegman PH, van Veen EB. Biobanking residual tissues. Hum Genet 2011;130(3):357-68.
29. Foundation Federation of Dutch Medical Scientific Societies. Human Tissue and Medical Research: Code of Conduct for responsible use. 2011, https://www.federa.org/sites/default/files/images/print_version_code_of_conduct_english.pdf.
30. van den Broek AJ, Schmidt MK, van 't Veer LJ, *et al.* Prognostic Impact of Breast-Conserving Therapy Versus Mastectomy of BRCA1/2 Mutation Carriers Compared With Noncarriers in a Consecutive Series of Young Breast Cancer Patients. Ann Surg 2019;270(2):364-372.
31. Buuren Sv. *Flexible imputation of missing data*. Boca Raton, FL: CRC Press; 2012.
32. Resche-Rigon M, White IR, Bartlett JW, *et al.* Multiple imputation for handling systematically missing confounders in meta-analysis of individual participant data. Stat Med 2013;32(28):4890-905.
33. Van Buuren S. *Flexible imputation of missing data*. Second ed: Chapman and Hall/CRC; 2018.
34. Geskus RB. Cause-specific cumulative incidence estimation and the fine and gray model under both left truncation and right censoring. Biometrics 2011;67(1):39-49.
35. Schoenfeld DA. Sample-size formula for the proportional-hazards regression model. Biometrics 1983;39(2):499-503.
36. Schmidt MK, Tollenaar RA, de Kemp SR, *et al.* Breast cancer survival and tumor characteristics in premenopausal women carrying the CHEK2*1100delC germline mutation. J Clin Oncol 2007;25(1):64-9.
37. Schmidt MK, Hogervorst F, van Hien R, *et al.* Age- and Tumor Subtype-Specific Breast Cancer Risk Estimates for CHEK2*1100delC Carriers. J Clin Oncol 2016;34(23):2750-60.
38. Steyerberg EW, Harrell FE, Jr. Prediction models need appropriate internal, internal-external, and external

validation. J Clin Epidemiol 2016;69:245-7.
39. Austin PC, van Klaveren D, Vergouwe Y, *et al.* Geographic and temporal validity of prediction models: different approaches were useful to examine model performance. J Clin Epidemiol 2016;79:76-85.
40. Collins GS, Ogundimu EO, Altman DG. Sample size considerations for the external validation of a multivariable prognostic model: a resampling study. Stat Med 2016;35(2):214-26.
41. Blanche P, Dartigues JF, Jacqmin-Gadda H. Estimating and comparing time-dependent areas under receiver operating characteristic curves for censored event times with competing risks. Stat Med 2013;32(30):5381-97.
42. Brentnall AR, Cuzick J. Risk Models for Breast Cancer and Their Validation. Stat Sci 2020;35(1):14-30.
43. Austin PC, Putter H, Giardiello D, *et al.* Graphical calibration curves and the integrated calibration index (ICI) for competing risk models. Diagn Progn Res 2022;6(1):2.
44. Collins GS, Reitsma JB, Altman DG, *et al.* Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD). Ann Intern Med 2015;162(10):735-6.
45. Vickers AJ, Elkin EB. Decision curve analysis: a novel method for evaluating prediction models. Med Decis Making 2006;26(6):565-74.
46. Kerr KF, Brown MD, Zhu K, *et al.* Assessing the Clinical Impact of Risk Prediction Models With Decision Curves: Guidance for Correct Interpretation and Appropriate Use. J Clin Oncol 2016;34(21):2534-40.
47. Vickers AJ, Cronin AM, Elkin EB, *et al.* Extensions to decision curve analysis, a novel method for evaluating diagnostic tests, prediction models and molecular markers. BMC Med Inform Decis Mak 2008;8:53.
48. Heemskerk-Gerritsen BA, Rookus MA, Aalfs CM, *et al.* Improved overall survival after contralateral risk-reducing mastectomy in BRCA1/2 mutation carriers with a history of unilateral breast cancer: a prospective analysis. Int J Cancer 2015;136(3):668-77.
49. Balmana J, Diez O, Rubio IT, *et al.* BRCA in breast cancer: ESMO Clinical Practice Guidelines. Ann Oncol 2011;22 Suppl 6:vi31-4.
50. Rutgers EJT. Is prophylactic mastectomy justified in women without BRCA mutation? Breast 2019;48 Suppl 1:S62-S64.
51. Giardiello D, Hauptmann M, Steyerberg EW, *et al.* Prediction of contralateral breast cancer: external validation of risk calculators in 20 international cohorts. Breast Cancer Res Treat 2020;181(2):423-434.
52. Antoniou AC, Pharoah PP, Smith P, *et al.* The BOADICEA model of genetic susceptibility to breast and ovarian cancer. Br J Cancer 2004;91(8):1580-90.
53. Antoniou AC, Cunningham AP, Peto J, *et al.* The BOADICEA model of genetic susceptibility to breast and ovarian cancers: updates and extensions. Br J Cancer 2008;98(8):1457-66.
54. Lee AJ, Cunningham AP, Tischkowitz M, *et al.* Incorporating truncating variants in PALB2, CHEK2, and ATM into the BOADICEA breast cancer risk model. Genet Med 2016;18(12):1190-1198.
55. Carver T, Hartley S, Lee A, *et al.* CanRisk Tool-A Web Interface for the Prediction of Breast and Ovarian Cancer Risk and the Likelihood of Carrying Genetic Pathogenic Variants. Cancer Epidemiol Biomarkers Prev 2021;30(3):469-473.
56. Kramer I, Schaapveld M, Oldenburg HSA, *et al.* The Influence of Adjuvant Systemic Regimens on Contralateral Breast Cancer Risk and Receptor Subtype. J Natl Cancer Inst 2019;111(7):709-718.
57. Witteveen A, Vliegen IM, Sonke GS, *et al.* Personalisation of breast cancer follow-up: a time-dependent prognostic nomogram for the estimation of annual risk of locoregional recurrence in early breast cancer patients. Breast Cancer Res Treat 2015;152(3):627-36.
58. Volkel V, Hueting TA, Draeger T, *et al.* Improved risk estimation of locoregional recurrence, secondary contralateral tumors and distant metastases in early breast cancer: the INFLUENCE 2.0 model. Breast Cancer Res Treat 2021; 10.1007/s10549-021-06335-z.
59. Nieboer D, Vergouwe Y, Ankerst DP, *et al.* Improving prediction models with new markers: a comparison of updating strategies. BMC Med Res Methodol 2016;16(1):128.
60. Madley-Dowd P, Hughes R, Tilling K, *et al.* The proportion of missing data should not be used to guide decisions on multiple imputation. J Clin Epidemiol 2019;110:63-73.
61. Collins GS, Altman DG. Predicting the 10 year risk of cardiovascular disease in the United Kingdom: independent and external validation of an updated version of QRISK2. BMJ 2012;344:e4181.
62. Breast Cancer Association C, Dorling L, Carvalho S, *et al.* Breast Cancer Risk Genes - Association Analysis in More than 113,000 Women. N Engl J Med 2021;384(5):428-439.
63. Ho WK, Tan MM, Mavaddat N, *et al.* European polygenic risk score for prediction of breast cancer shows similar performance in Asian women. Nat Commun 2020;11(1):3833.
64. Evans DG, van Veen EM, Byers H, *et al.* The importance of ethnicity: Are breast cancer polygenic risk scores ready for women who are not of White European origin? Int J Cancer 2021; 10.1002/ijc.33782.
65. Christodoulou E, Ma J, Collins GS, *et al.* A systematic review shows no performance benefit of machine learning over logistic regression for clinical prediction models. J Clin Epidemiol 2019;110:12-22.
66. Giardiello D, Antoniou AC, Mariani L, *et al.* Letter to the editor: a response to Ming's study on machine learning techniques for personalized breast cancer risk prediction. Breast Cancer Res 2020;22(1):17.
67. Thompson D, Easton D. The genetic epidemiology of breast cancer genes. J Mammary Gland Biol Neoplasia 2004;9(3):221-36.
68. Reiner AS, Sisti J, John EM, *et al.* Breast Cancer Family History and Contralateral Breast Cancer Risk in Young Women: An Update From the Women's Environmental Cancer and Radiation Epidemiology Study. J Clin Oncol 2018;36(15):1513-1520.
69. Torkamani A, Wineinger NE, Topol EJ. The personal and clinical utility of polygenic risk scores. Nat Rev Genet 2018;19(9):581-590.
70. Wald NJ, Old R. The illusion of polygenic disease risk prediction. Genet Med 2019; 10.1038/s41436-018-0418-5.
71. Knight JA, Blackmore KM, Fan J, *et al.* The association of mammographic density with risk of contralateral breast cancer and change in density with treatment in the WECARE study. Breast Cancer Res 2018;20(1):23.
72. Van Belle V, Van Calster B. Visualizing Risk Prediction Models. PLoS One 2015;10(7):e0132614.
73. Bonnett LJ, Snell KIE, Collins GS, *et al.* Guide to presenting clinical prediction models for use in clinical settings. BMJ 2019;365:l737.

SUPPLEMENTARY MATERIALS

1. Data and patient selection

For this study we used data from six main sources available from national and international collaborations including nationwide registry data, as well as hospital-based studies with more detailed information on relevant prediction factors[1-5]. Briefly, the six main sources were: (1) The Breast Cancer Association Consortium (BCAC), which is an international consortium of 106 studies comprising 186,594 patients (data version August 2019) with a primary breast cancer (BC) diagnosed between 1939 and 2018[1]. In our previous study, 16 studies were selected to develop PredictCBC models. In this study, two studies were additionally included in the dataset to develop PredictCBC-2.0 models[6]; (2) The Amsterdam Breast Cancer Study (ABCS) containing 2,763 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 7,105 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 including 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 who 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 2015, a period for which sufficient follow-up and receptor status information were available[4, 5];(6) Hereditary Breast and Ovarian cancer study, the Netherlands (HEBON) study is an ongoing nationwide Dutch study among members of *BRCA1/2* families in the Netherlands, including 16,617 BC patients diagnosed between 1953 and 2017[7]. The general design includes a retrospective cohort because the *BRCA1/2* DNA test was available from 1995, with a prospective follow-up. *BRCA1/2* families were identified through ten centers (nine Clinical Genetic Centers/Family Cancer Clinics and the Foundation for the Detection of Hereditary Tumors). 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, *CHEK2* c.1100delC, polygenic risk score (PRS) (derived from BCAC), body mass index (BMI), parity 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[2, 8, 9]. 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 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 **Supplementary Table 2**. Follow-up started three months after invasive first primary BC diagnosis, to exclude synchronous contralateral breast cancer (CBC), and ended at date of CBC, distant metastasis (but not 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 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.

Age at first primary BC seemed to have a non-linear relation with CBC. Using splines, we observed that CBC risk increased with age till around 60 years old and declined afterwards. Therefore, we used a linear spline with a knot at 60 years in the prediction model. The use of this linear spline was a good compromise to address the non-linear relation 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 relation resembled the shape of age-related BC incidence curves with an increased risk until menopausal age followed by a decrease (Clemmensen's hook)[10].

2. Multiple imputation of missing values

The percentage of missing values across the predictors varied between 3.2% and 84% 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[11-13].

For our analyses, we used five 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 IPD from multiple studies[13]. Continuous, binary, and multiple categorical variables were imputed using predictive mean matching, binary and multinomial logistic regression, respectively. Time-to-event outcome defined as time to CBC, time to death, and time to distant metastasis were included in the imputation process through the Nelson-Aalen cumulative hazard estimator[14]. 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. 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 (ductal and lobular)' and 'Other'). After multiple imputation, we created two categories 'Lobular including mixed' and 'Ductal including other' to mitigate possible overfitting due to the small numbers of patients with '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, 1% of patients with 97 CBC events were coded as ER-negative treated with endocrine therapy and 0.1% of patients with 11 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 (67%) were ER-positive treated with endocrine therapy and 60% were HER2-positive treated with trastuzumab in the complete data.

We used the R package mice (version 3.13.0) to impute our data and combine the estimates using Rubin's rules.

3. Formula to estimate the contralateral breast cancer risk using PredictCBC-2.0A

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. To calculate the predicted CBC cumulative incidence, we used the event-free baseline probability of the Dutch Cancer Registry. The baseline survival estimates according to the model and time *t* are:

$S_0(5) = 0.985$

$S_0(10) = 0.971$

And

Linear Predictor (LP) =

– 0.303 + 0.003× Age – 0.031 × Age' + 0.011 × BMI – 0.0812 × Parity + 0.157 × I[Family history = Yes] + 1.566 × I[*BRCA* = *BRCA1*] + 1.128 × I[*BRCA* = *BRCA2*] + 0.938 × I[*CHEK2* c.1100delC] + 0.398 × PRS-313 – 0.011 × I[Nodal status = positive] – 0.089 × I[Size of PBC = (2,5] *cm*] + 0.201 × I[Size of PBC = greater than 5 *cm*] + 0.186 × I[Morphology of PBC = lobular including mixed] – 0.069 × I[Grade of PBC = moderately differentiated] – 0.163 × I[Grade of PBC = poorly/undifferentiated]– 0.285 × I[Chemotherapy = yes] + 0.065 × I[Radiotherapy to the breast = yes] + 0.428 × I[ER-negative without endocrine therapy] + 0.668 × I[ER-positive without endocrine therapy]+ 0.203 × I[HER2-negative without trastuzumab] + 0.111 × I[HER2-positive without trastuzumab]

Where Age' = max(Age – 60, 0), with age in years

4. Formula to estimate the contralateral breast cancer risk in using PredictCBC-2.0B

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

$S_0(5) = 0.984$

$S_0(10) = 0.970$

And

– 0.160 – 0.002 × Age – 0.029 × Age' + 0.011 × BMI – 0.0728 × Parity + 0.304 × I[Family history = Yes] – 0.013× I[Nodal status = positive] + 0.011 × I[Size of PBC = (2,5] *cm*] + 0.198 × I[Size of PBC = greater than 5 *cm*] + 0.158 × I[Morphology of PBC = lobular including mixed] – 0.017 × I[Grade of PBC = moderately differentiated] – 0.055 × I[Grade of PBC = poorly/undifferentiated]– 0.293 × I[Chemotherapy = yes] – 0.055 × I[Radiotherapy to the breast = yes] + 0.578 × I[ER-negative without endocrine therapy] + 0.661 × I[ER-positive without endocrine therapy]+ 0.262 × I[HER2-negative without trastuzumab] + 0.133 × I[HER2-positive without trastuzumab]

Where Age' = max(Age – 60, 0), with age in years.

Supplementary Table 1: Patient characteristics in the different data sources.

	Source of data					
	ABCS	BCAC‡	BOSOM	EMC	HEBON	NCR
Number of patients	2,763	186,594	7,105	3,483	16,617	160,861
Eligibility criteria, *number of patients excluded*						
Studies from Asian countries	-	7,146	-	-	-	-
Patients of non-European descent	74	51,328	-	-	-	-
Patients younger than 18 years old	-	4	-	-	-	-
Year of PBC diagnosis before 1990	-	4,014	3,126	-	1,132	-
Year of PBC diagnosis missing	-	15,435	-	-	2	-
PBC stage 0	123	38	2	-	-	-
PBC stage IV	149	1,811	104	-	115	7,774
Patients did not undergo surgery	24	1,247	43	5	293	9,278
Number of eligible patients	2,393	105,571	3,830	3,478	15,075	143,809
No follow-up or follow-up less than 3 months	173	15,804	70	88	2,382*	3,396
Familiar breast cancer studies	-	6,739	-	-	-	-
Studies with less than 10 CBC events	-	37,994	-	-	-	-
Number of patients included in the analysis (number of patients with CBC)	2,220 (44)	45,034 (1,001)	3,760 (288)	3,390 (221)	12,693 (918)	140,413 (5,753)
Total number of patients included in the analysis (number of CBC)	207,510 (8,225 of which 6,828 invasive and 1,397 in situ)					

Abbreviations:
ABCS: Amsterdam Breast Cancer Study; BCAC: Breast Cancer Association Consortium. ‡BCAC is composed of 106 studies world-wide. The 45,034 patients selected for the analysis came from 18 studies; BOSOM: Breast Cancer Outcome Study of Mutation carriers; EMC: Erasmus Medical Center; HEBON: Hereditary Breast and Ovarian cancer study Netherlands. *1,433 tested for *BRCA1/2* germline mutation after CBC or preventive mastectomy; NCR: Netherlands Cancer Registry; PBC: primary breast cancer; CBC: contralateral breast cancer

Supplementary Table 2: available online.

Supplementary Table 3: 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.

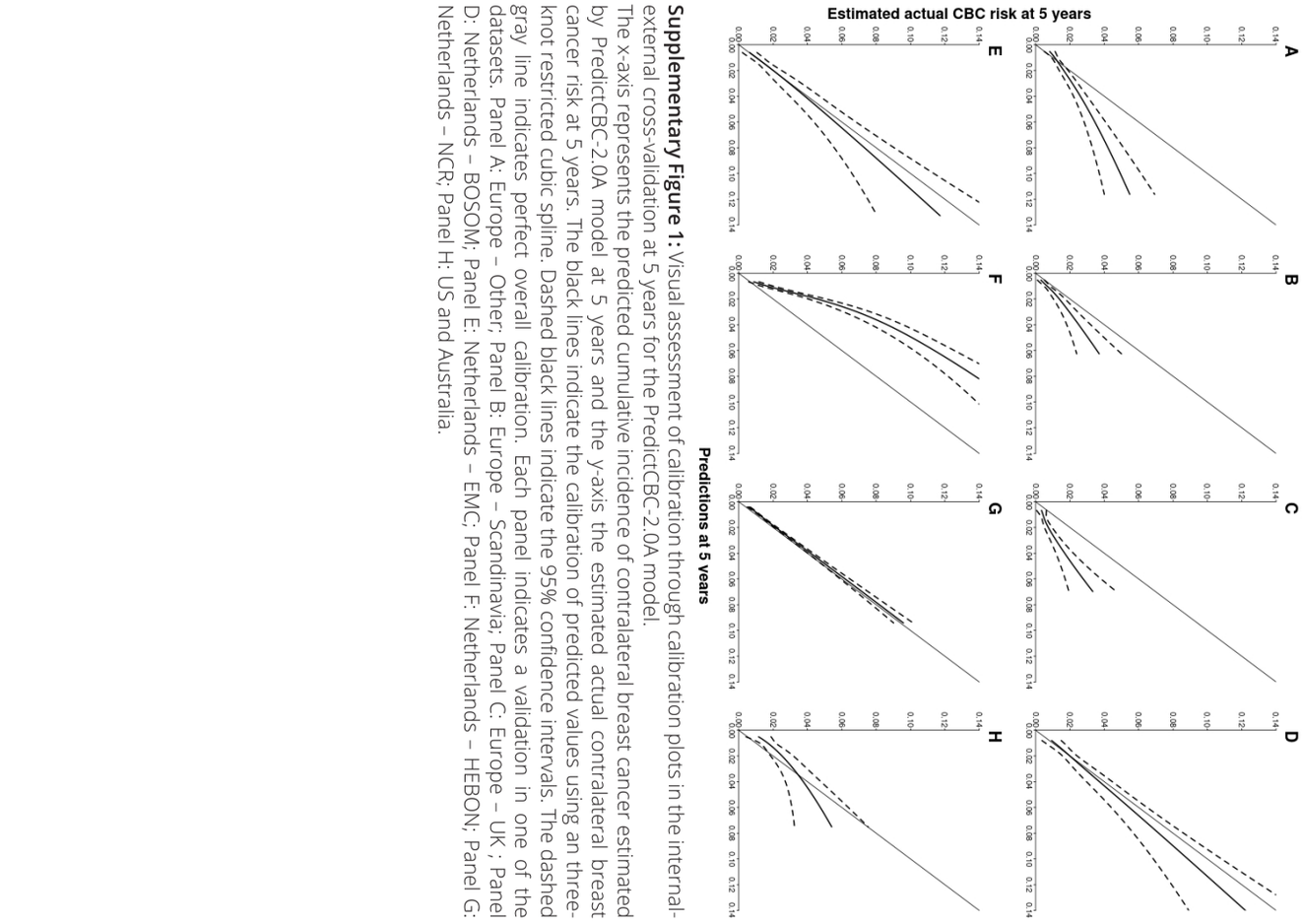
Study	Country	Geographic area or study
ABCS	Netherlands	Europe - Other
ABCFS	Australia	United States and Australia
BBCC	Germany	Europe - Other
BREOGAN	Spain	Europe - Other
CGPS	Denmark	Europe - Scandinavia
HEBCS	Finland	Europe - Scandinavia
KARBAC	Sweden	Europe - Scandinavia
KARMA	Sweden	Europe - Scandinavia
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
UBCS	United States	United States and Australia

Supplementary Table 4: available online (Patient and primary breast cancer characteristics per study).

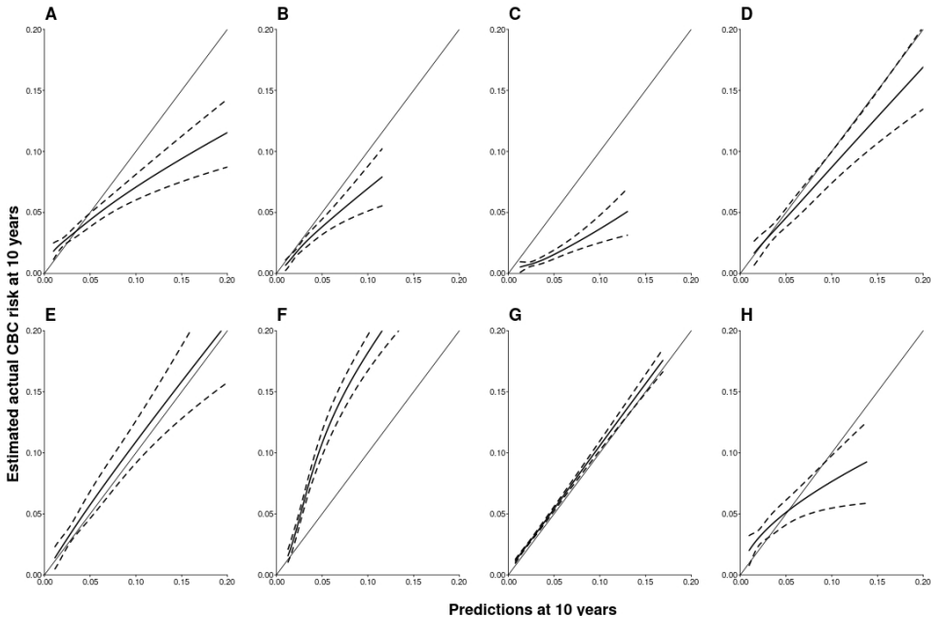
Supplementary Table 5: Clinical utility of the 5-year contralateral breast cancer risk prediction models (PredictCBC-1A with PredictCBC-2.0A and PredictCBC-1B with PredictCBC-2.0B). For PredictCBC versions 1A and 2.0A, at the same probability threshold, the net benefit is exemplified in *BRCA1/2* mutation carriers (for avoiding unnecessary CPM) and non-carriers (performing necessary CPM). For PredictCBC versions 1B and 2.0B, 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).

PredictCBC-1A and PredictCBC-2.0A							
		BRCA1/2 mutation carriers			Non-carriers		
Probability threshold p_t (%)	Unnecessary CPMs needed to detect one necessary CPM*	Net benefit versus treat all patients with CPM (per 1000)	Avoided unnecessary CPMs per 1000 patients using PredictCBC-1A	Additional avoided unnecessary CPMs per 1000 patients using PredictCBC-2.0A	Net benefit versus treat none (per 1000)	Performed necessary CPMs per 1000 patients using PredictCBC-1A	Additional performed necessary CPMs per 1000 patients using PredictCBC-2.0A
3	32.3	0.2	6.0	0.0	0.6	19.7	210.9
4	24.0	1.9	44.4	16.4	No benefit	0.0	129.4
5	19.0	3.4	64.1	66.7	No benefit	0.0	56.9
6	15.7	9.4	146.6	34.1	No benefit	0.0	0.0
PredictCBC-1B and PredictCBC-2.0B							
		Family history			No family history		
Probability threshold p_t (%)	Unnecessary CPMs needed to detect one necessary CPM*	Net benefit versus treat all patients with CPM (per 1000)	Avoided unnecessary CPMs per 1000 patients using PredictCBC-1B	Additional avoided unnecessary CPMs per 1000 patients using PredictCBC-2.0B	Net benefit versus treat none (per 1000)	Performed necessary CPMs per 1000 patients using PredictCBC-1B	Additional performed necessary CPMs per 1000 patients using PredictCBC-2.0B
2	49	2.3	115.1	0.0	3.4	168.1	0.0
2.5	39	5.7	200.4	0.0	1.8	70.1	0.0
3	32.3	3.6	258.3	0.0	0.6	19.9	0.3

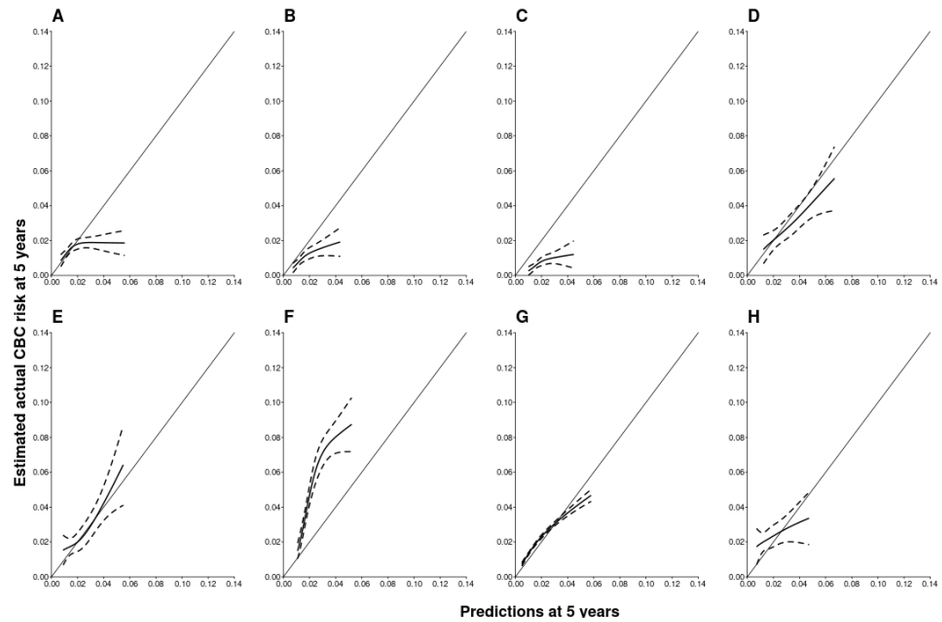
CPM: contralateral preventive mastectomy;
* The number of unnecessary contralateral mastectomies needed to detect one necessary CPM is calculated by: (1-pt)/pt



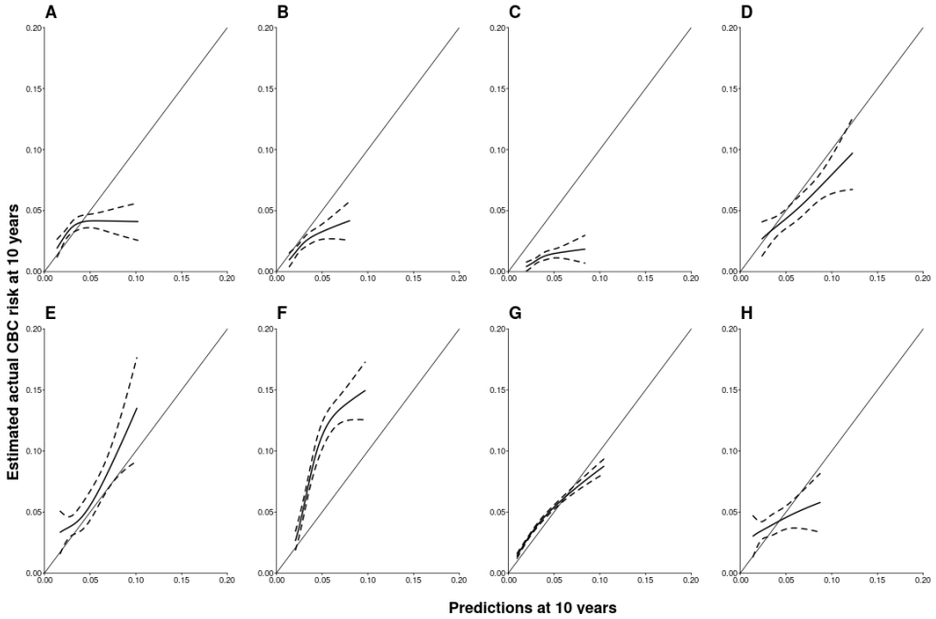
Supplementary Figure 1: Visual assessment of calibration through calibration plots in the internal-external cross-validation at 5 years for the PredictCBC-2.0A model.
The x-axis represents the predicted cumulative incidence of contralateral breast cancer estimated by PredictCBC-2.0A model at 5 years and the y-axis the estimated actual contralateral breast cancer risk at 5 years. The black lines indicate the calibration of predicted values using an three-knot restricted cubic spline. Dashed black lines 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: Europe – Other; Panel B: Europe – Scandinavia; Panel C: Europe – UK ; Panel D: Netherlands – BOSOM; Panel E: Netherlands – EMC; Panel F: Netherlands – HEBON; Panel G: Netherlands – NCR; Panel H: US and Australia.



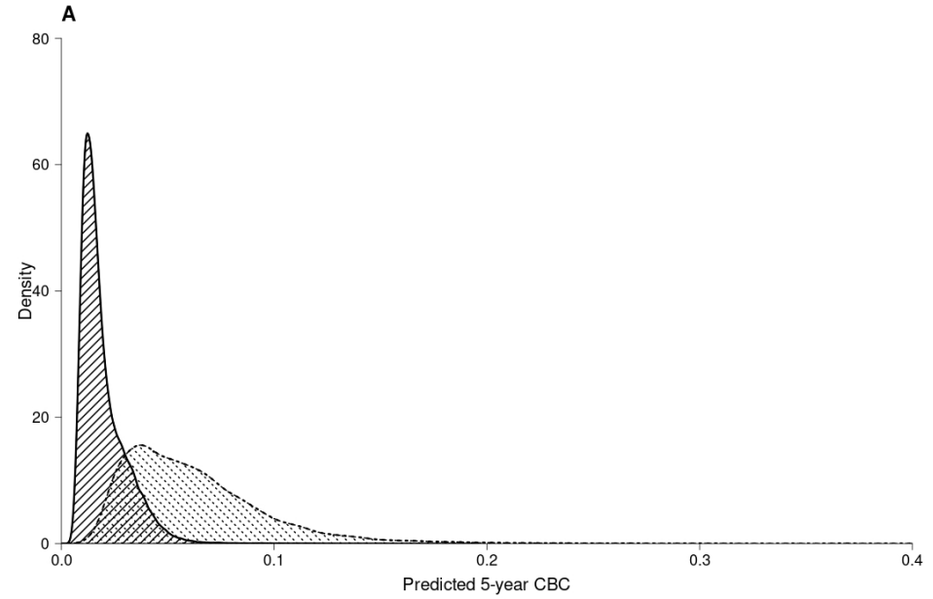
Supplementary Figure 2: Visual assessment of calibration through calibration plots in the internal-external cross-validation at 10 years for the PredictCBC-2.0A model.
The x-axis represents the predicted cumulative incidence of contralateral breast cancer estimated by PredictCBC-2.0A model at 10 years and the y-axis the estimated actual contralateral breast cancer risk at 10 years. The black lines indicate the calibration of predicted values using a three-knot restricted cubic spline. Dashed black lines 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: Europe – Other; Panel B: Europe – Scandinavia; Panel C: Europe – UK; Panel D: Netherlands – BOSOM; Panel E: Netherlands – EMC; Panel F: Netherlands – HEBON; Panel G: Netherlands – NCR; Panel H: US and Australia.



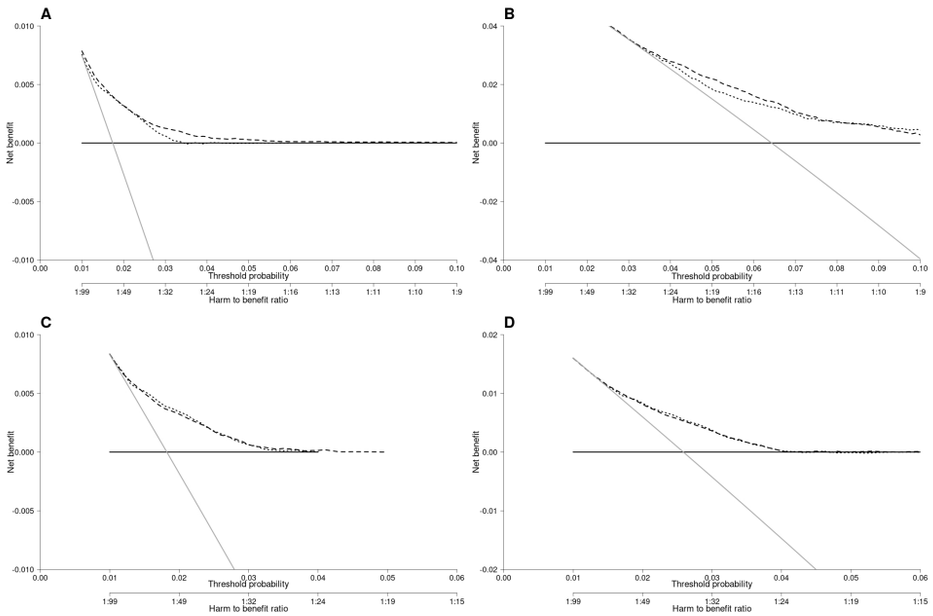
Supplementary Figure 3: Visual assessment of calibration through calibration plots in the internal-external cross-validation at 5 years for the PredictCBC-2.0B model.
The x-axis represents the predicted cumulative incidence of contralateral breast cancer estimated by PredictCBC-2.0B model at 5 years and the y-axis the estimated actual contralateral breast cancer risk at 5 years. The black lines indicate the calibration of predicted values using a three-knot restricted cubic spline. Dashed black lines 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: Europe – Other; Panel B: Europe – Scandinavia; Panel C: Europe – UK; Panel D: Netherlands – BOSOM; Panel E: Netherlands – EMC; Panel F: Netherlands – HEBON; Panel G: Netherlands – NCR; Panel H: US and Australia.



Supplementary Figure 4: Visual assessment of calibration through calibration plots in the internal-external cross-validation at 10 years for the PredictCBC-2.0B model.
The x-axis represents the predicted cumulative incidence of contralateral breast cancer estimated by PredictCBC-2.0B model at 10 years and the y-axis the estimated actual contralateral breast cancer risk at 10 years. The black lines indicate the calibration of predicted values using an three-knot restricted cubic spline. Dashed black lines 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: Europe – Other; Panel B: Europe – Scandinavia; Panel C: Europe – UK; Panel D: Netherlands – BOSOM; Panel E: Netherlands – EMC; Panel F: Netherlands – HEBON; Panel G: Netherlands – NCR; Panel H: US and Australia.



Supplementary Figure 5: Density distribution of 5-year predicted contralateral breast cancer using PredictCBC-2.0 models. **a** Density distribution of 5-year predicted contralateral breast cancer absolute risk using PredictCBC-2.0A within non-carriers (area with black solid lines) and *BRCA1/2* mutation carriers (area with black dashed lines). **b** Density distribution of 5-year predicted contralateral breast cancer absolute risk using PredictCBC-2.0B within patients without (first degree) family history (area with black solid lines) and patients with (first degree) family history (area with black dashed lines).



Supplementary Figure 6. Decision curve analysis at 5 years for the contralateral breast cancer risk models (PredictCBC and PredictCBC-2.0) including *BRCA* mutation information. **a** 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 PredictCBC-1A (dotted black line) and PredictCBC-2.0A (dashed black line) compared to not treating any patients with contralateral preventive mastectomy (CPM) (black solid line). **b** The decision curve to determine the net benefit of the estimated 5-year predicted CBC cumulative incidence for *BRCA1/2* mutation carriers using PredictCBC-1A (dotted black line), PredictCBC-2.0A (dashed black line) versus treating (or at least counseling) all patients (gray solid line). **c** The decision curve to determine the net benefit of the estimated 5-year predicted CBC cumulative incidence for patients without (first-degree) family history using PredictCBC-1B (dotted black line), PredictCBC-2.0B (dashed black line) compared to not treating any patients with CPM (black solid line). **d** The decision curve to determine the net benefit of the estimated 5-year predicted CBC cumulative incidence for patients with (first-degree) family history using PredictCBC-1B (dotted black line), PredictCBC-2.0B (dashed black line) versus treating (or at least counseling) all patients (gray 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., 5%). The x-axis represents the threshold probability. Using a threshold probability of 5% implicitly means that CPM in 20 patients of whom one would develop a CBC if untreated is acceptable (19 unnecessary CPMs, harm to benefit ratio 1:19)

REFERENCES

1. Michailidou K, Lindstrom S, Dennis J, *et al.* Association analysis identifies 65 new breast cancer risk loci. Nature 2017;551(7678):92-94.
2. Schmidt MK, Tollenaar RA, de Kemp SR, *et al.* Breast cancer survival and tumor characteristics in premenopausal women carrying the CHEK2*1100delC germline mutation. J Clin Oncol 2007;25(1):64-9.
3. Schmidt MK, van den Broek AJ, Tollenaar RA, *et al.* Breast Cancer Survival of BRCA1/BRCA2 Mutation Carriers in a Hospital-Based Cohort of Young Women. J Natl Cancer Inst 2017;109(8).
4. Font-Gonzalez A, Liu L, Voogd AC, *et al.* Inferior survival for young patients with contralateral compared to unilateral breast cancer: a nationwide population-based study in the Netherlands. Breast Cancer Res Treat 2013;139(3):811-9.
5. Kramer I, Schaapveld M, Oldenburg HSA, *et al.* The influence of adjuvant systemic regimens on contralateral breast cancer risk and receptor subtype. J Natl Cancer Inst In press.
6. Giardiello D, Steyerberg EW, Hauptmann M, *et al.* Prediction and clinical utility of a contralateral breast cancer risk model. Breast Cancer Res 2019;21(1):144.
7. Pijpe A, Manders P, Brohet RM, *et al.* Physical activity and the risk of breast cancer in BRCA1/2 mutation carriers. Breast Cancer Res Treat 2010;120(1):235-44.
8. Mavaddat N, Michailidou K, Dennis J, *et al.* Polygenic Risk Scores for Prediction of Breast Cancer and Breast Cancer Subtypes. Am J Hum Genet 2019;104(1):21-34.
9. Kramer I, Hooning MJ, Mavaddat N, *et al.* Breast Cancer Polygenic Risk Score and Contralateral Breast Cancer Risk. Am J Hum Genet 2020;107(5):837-848.
10. Bouchardy C, Usel M, Verkooijen HM, *et al.* Changing pattern of age-specific breast cancer incidence in the Swiss canton of Geneva. Breast Cancer Res Treat 2010;120(2):519-23.
11. Riley RD, Lambert PC, Abo-Zaid G. Meta-analysis of individual participant data: rationale, conduct, and reporting. BMJ 2010;340:c221.
12. Resche-Rigon M, White IR, Bartlett JW, *et al.* Multiple imputation for handling systematically missing confounders in meta-analysis of individual participant data. Stat Med 2013;32(28):4890-905.
13. Jolani S, Debray TP, Koffijberg H, *et al.* Imputation of systematically missing predictors in an individual participant data meta-analysis: a generalized approach using MICE. Stat Med 2015;34(11):1841-63.
14. White IR, Royston P. Imputing missing covariate values for the Cox model. Stat Med 2009;28(15):1982-98.