Prediction of contralateral breast cancer: statistical aspects and prediction performance
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Chapter 3

**Prediction of contralateral breast cancer:
External validation of risk calculators in
20 international cohorts**

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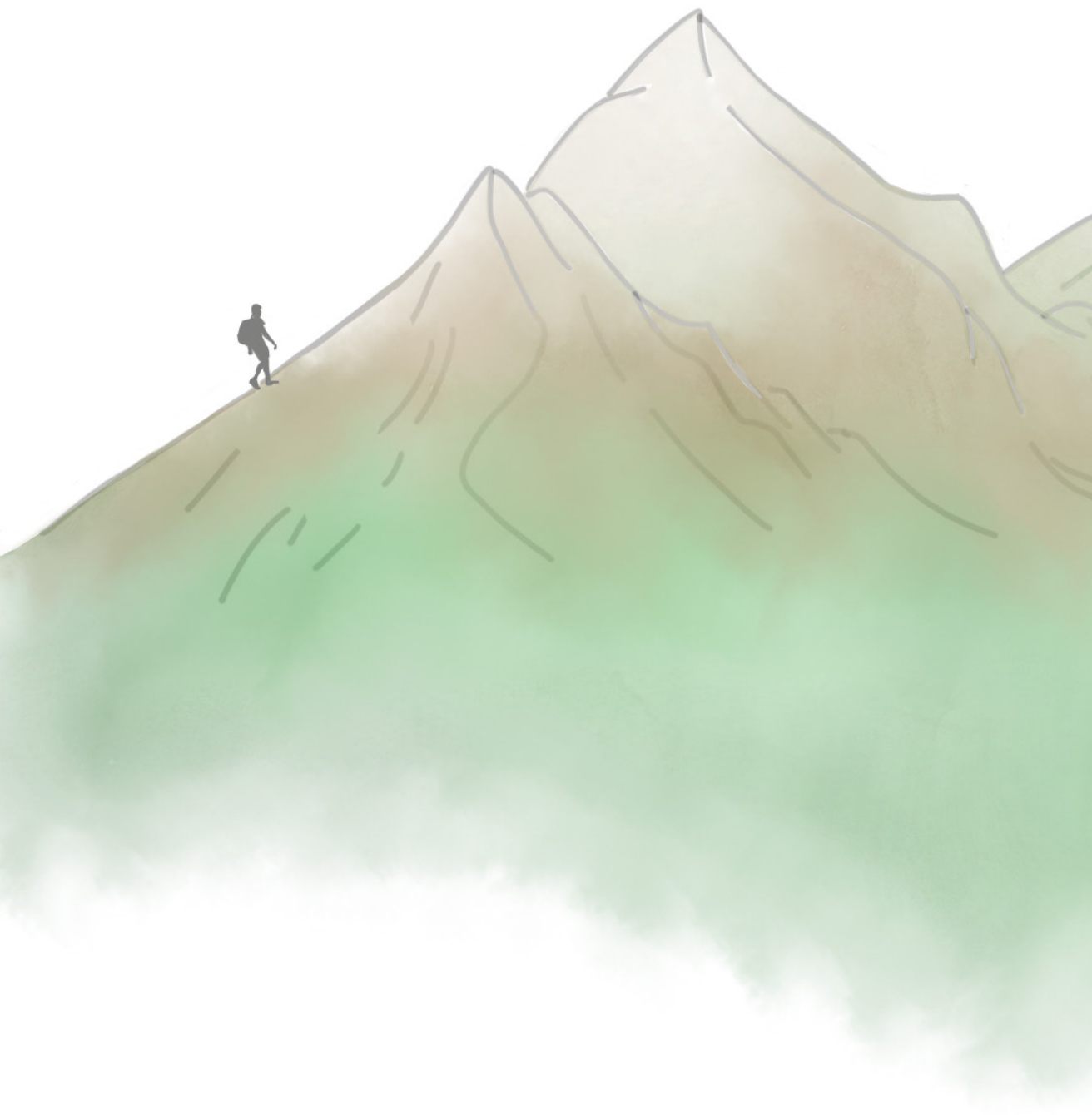
ABSTRACT

Background
Three tools are currently available to predict the risk of contralateral breast cancer (CBC). We aimed to compare the performance of the Manchester formula, CBCrisk, and PredictCBC in patients with invasive breast cancer (BC).

Methods
We analyzed data of 132,756 patients (4,682 CBC) from 20 international studies with a median follow-up of 8.8 years. Prediction performance included discrimination, quantified as a time-dependent Area-Under-the-Curve (AUC) at 5 and 10 years after diagnosis of primary BC, and calibration, quantified as the expected-observed (E/O) ratio at 5 and 10 years and the calibration slope.

Results
The AUC at 10 years was: 0.58 (95% confidence intervals [CI]: 0.57–0.59) for CBCrisk; 0.60 (95%CI: 0.59–0.61) for the Manchester formula; 0.63 (95%CI: 0.59–0.66) and 0.59 (95%CI: 0.56–0.62) for PredictCBC-1A (for settings where *BRCA1/2* mutation status is available) and PredictCBC-1B (for the general population), respectively. The E/O at 10 years: 0.82 (95%CI: 0.51–1.32) for CBCrisk; 1.53 (95%CI: 0.63–3.73) for the Manchester formula; 1.28 (95%CI: 0.63–2.58) for PredictCBC-1A and 1.35 (95%CI: 0.65–2.77) for PredictCBC-1B. The calibration slope was 1.26 (95%CI: 1.01–1.50) for CBCrisk; 0.90 (95%CI: 0.79–1.02) for PredictCBC-1A; 0.81 (95%CI: 0.63–0.99) for PredictCBC-1B, and 0.39 (95%CI: 0.34–0.43) for the Manchester formula.

Conclusions
Current CBC risk prediction tools provide only moderate discrimination and the Manchester formula was poorly calibrated. Better predictors and re-calibration are needed to improve CBC prediction and to identify low and high CBC risk patients for clinical decision making.

Keywords
Contralateral breast cancer, risk prediction, validation, clinical decision making

INTRODUCTION

A rising number of women with breast cancer (BC) are at risk to develop a new primary tumor in the contralateral breast (CBC) with consequently another cancer treatment and potentially less favorable prognosis[1]. Although CBC incidence is low (~0.4% per year) in the general BC population, contralateral preventive mastectomy (CPM) is increasing, also among women with low CBC risk[2-5].

Three tools are tools currently available to predict the risk of CBC, although probably none are widely used: 1) the Manchester formula; 2) CBCrisk, and 3) PredictCBC[6-8]. The Manchester group in the United Kingdom (UK) proposed a set of guidelines for counseling women about CPM[8]. Based on a systematic review of the literature, they devised a formula to estimate lifetime CBC risk based on age at first primary BC, family history of BC, estrogen-receptor (ER) status, diagnosis of ductal carcinoma in situ (DCIS), and oophorectomy.

The second tool, CBCrisk, was developed using data on 1,921 CBC cases and 5,763 matched controls with primary BC[7]. The model uses data on age at first BC diagnosis, age at first birth, first degree family history of BC, high-risk pre-neoplasia, breast density (obtained using the BI-RADS system), ER status, first BC type (pure invasive, pure DCIS, a mix of the two, unknown), and adjuvant endocrine therapy. External validation was performed using two independent studies in the United States (US) of 5,185 and 6,035 patients with 111 and 117 CBC events[7,9]. A web-based application provides individualized prediction of CBC risk[10].

Third, PredictCBC was developed, cross-validated and evaluated using data from 132,756 patients with first BC and 4,672 CBC events, as part of an international collaboration[5]. PredictCBC predicts CBC risk as a function of family history (first degree) of primary BC, and information of primary BC diagnosis: age, nodal status, size, grade, morphology, ER status, human epidermal growth factor receptor 2 (HER2) status, administration of adjuvant or neoadjuvant chemotherapy, adjuvant endocrine therapy, adjuvant trastuzumab therapy, and radiotherapy. Two versions were developed: PredictCBC version 1A includes presence or absence of a mutation in the *BRCA1* or *BRCA2* genes, an important determinant of CBC[5,11,12], while PredictCBC version 1B was developed for untested patients.

External validation in different studies is relevant to assess the prediction performance of prediction models[13]. Our aim was to perform a head-to-head comparison between CBCrisk, PredictCBC and the Manchester formula. We hereto used several large population- and hospital-based studies used to develop and cross-validate the PredictCBC models.

MATERIAL AND METHODS

External validation of CBCrisk and the Manchester formula was performed in 20 studies: four with individual patient data from the Netherlands (the Amsterdam Breast Cancer Study (ABCS), the Breast Cancer Outcome Study of Mutation carriers (BOSOM), the Erasmus MC Breast Cancer Registry (EMC), the Netherlands Cancer Registry (NCR)); and 16 other studies of the Breast Cancer Association Consortium (BCAC). The latter is an international consortium of 102 studies comprising 182,898 patients (data version: January 2017) with a primary BC diagnosed between 1939 and 2016[14]. Of these, 16 non-familial BC BCAC studies including invasive non-metastatic European-descent female patients with first primary invasive BC diagnosed from 1990 onwards, and with at least 10 CBC events, were included in the analyses[14]. Details about studies and patient selection, and data imputation were described previously[5].

The outcome was in situ or invasive 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 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. In the BCAC, 27,155 patients were recruited more than 3 months after diagnosis of the first primary BC (prevalent cases); for these patients, follow-up started at date of recruitment (left truncation). Distant metastasis and death due to any cause were competing events.

The Manchester formula provides an estimate of a woman's individual life-time CBC risk. To assess the prediction performance, we translated the life-time CBC risk to 5- and 10-year CBC risks (see **Supplementary Material**). The predictors included in the CBC risk estimation in the Manchester formula, CBCrisk and PredictCBC models are provided in **Table 1**. Predictors that were sporadically missing were multiply imputed as described elsewhere[5].

Statistical analysis
Discrimination, the ability of the model to differentiate between patients who experienced CBC and those who did not, was calculated by time-dependent Area-Under-the-Curve (AUCs) based on Inverse Censoring Probability Weighting at 5 and 10 years[15,16]. Values of AUCs close to 1 indicate good discrimination while values close to 0.5 indicate poor discrimination (a coin flip). Calibration is the agreement between observed and predicted risk and is commonly characterized by calibration-in-the-large and slope statistic. Calibration-in-the-large characterizes the overall difference between the observed and predicted risks. It was calculated using the expected/observed (E/O) ratio. An E/O less than 1 indicates that the model systematically underestimates CBC risk, while an E/O above 1 indicates that the model systematically overestimates CBC risk. The expected

number of cases was calculated by summing the individual predicted probabilities at 5 and 10 years, based on the patient-specific covariate values[17]. The observed number of cases was estimated by the non-parametric CBC cumulative incidence at 5 and 10 years. The calibration slope was estimated using a Fine and Gray regression model using the linear predictor of the prediction tools. The linear predictor was vs constructed as the sum of the factors included in each model weighted by the corresponding regression coefficients (or parameters), and then computed in the validation dataset exactly as reported for the development set. The calibration slope is determined as the regression coefficient for this linear predictor when fitted as a single covariate in a regression model of disease outcome in the validation dataset. A well-calibrated model should have a calibration slope of 1; slopes < 1 indicate that coefficients were too optimistic for the validation setting[18]. Calibration results were graphically displayed.

Table 1: Predictors included in current contralateral breast cancer risk prediction tools

List of predictors	CBCrisk§	Manchester formula†	PredictCBC version 1A‡	PredictCBC version 1B‡
Age at diagnosis	✓	✓	✓	✓
Age at first birth	✓			
First-degree family history	✓	✓	✓	✓
BRCA1/2 germline mutation		✓	✓	
First breast cancer behavior type*	✓	✓		
Lymph node status			✓	✓
Breast density	✓			
Tumor size			✓	✓
Morphology			✓	✓
Tumor grade			✓	✓
High risk pre-neoplasia	✓			
ER status	✓	✓	✓	✓
HER2 status			✓	✓
Chemotherapy			✓	✓
Endocrine therapy	✓		✓	✓
Radiation to the breast			✓	✓
Trastuzumab			✓	✓
Oophorectomy under 40 years		✓		

* Contralateral breast cancer risk was calculated including women diagnosed with ductal carcinoma in situ;
§Chowdhury M, Euhus D, Onega T, Biswas S, Choudhary PK (2017) A model for individualized risk Abbreviation: ER: estrogen receptor status; HER2: human epidermal growth factor receptor 2.
prediction of contralateral breast cancer. Breast Cancer Res Treat 161 (1):153-160.
†Basu NN, Ross GL, Evans DG, Barr L (2015) The Manchester guidelines for contralateral risk-reducing mastectomy. World J Surg Oncol 13:237
‡ Giardiello D, Steyerberg EW, Hauptmann M, Adank MA, Akdeniz D, Blomqvist C, Bojesen SE, Bolla MK, Brinkhuis M, Chang-Claude J, Czene K, Devilee P, Dunning AM, Easton DF, Eccles DM, Fasching PA, Figueroa J, Flyger H, Garcia-Closas M, Haeberle L, Haiman CA, Hall P, Hamann U, Hopper JL, Jager A, Jakubowska A, Jung A, Keeman R, Kramer I, Lambrechts D, Le Marchand L, Lindblom A, Lubinski J, Manoochehri M, Mariani L, Nevanlinna H, Oldenburg HSA, Pelders S, Pharoah PDP, Shah M, Siesling S, Smit V, Southey MC, Tapper WJ, Tollenaar R, van den Broek AJ, van Deurzen CHM, van Leeuwen FE, van Ongeval C, Van't Veer LJ, Wang Q, Wendt C, Westenend PJ, Hooning MJ, Schmidt MK (2019) Prediction and clinical utility of a contralateral breast cancer risk model. Breast Cancer Res 21 (1):144. doi:10.1186/s13058-019-1221-1

Analyses were stratified by geographic groups of studies, since stratification by individual studies would provide too few events in some strata[13,19,5]. To allow for heterogeneity across multiple studies, random-effect meta-analyses were performed. We calculated 95% confidence intervals (CI) and 95% prediction intervals (PI), which indicate the likely range for prediction accuracy of the model in a new dataset, for discrimination and calibration measures. A sensitivity analysis was performed to check the consistency of CBCrisk performance measures when metachronous CBC was defined as an event after 6 instead of 3 months since the first BC diagnosis. More details are provided in the **Supplementary Material**. All analyses were implemented using SAS (SAS Institute Inc., NC, USA) and R software[20].

RESULTS

We included 132,756 patients from 20 studies who experienced 4,862 CBC events during a median follow-up of 8.8 years. The main patient and clinical characteristics across studies and geographic areas are shown in **Table 2**.

The AUCs at 5 and 10 years was around 0.6: 0.59 (95% CI: 0.57–0.61; 95% PI: 0.54–0.64) and 0.58 (95% CI: 0.57–0.59; 95% PI: 0.55–0.61) for CBCrisk (**Figure 1**); 0.61 (95% CI: 0.60–0.62; 95% PI: 0.59–0.63) and 0.60 (95% CI: 0.59–0.61; 95% PI: 0.58–0.62) for the Manchester formula (**Figure 2**). The E/O ratio at 5 and 10 years was close to 1 for all models: 0.86 (95% CI: 0.50–1.46; 95% PI: 0.20–3.75) and 0.82 (95% CI: 0.51–1.32; 95% PI: 0.21–3.14) for CBCrisk **(Table 3)**; 1.54 (95% CI: 0.61–3.92; 95% PI: 0.11–20.72, **Table 4**), and 1.53 (95% CI: 0.63–3.73; 95% PI: 0.13–18.52) for the Manchester formula (**Table 4**); 1.26 (95% CI: 0.57–2.77; 95% PI: 0.14–11.34), and 1.28 (95% CI: 0.63–2.58; 95% PI: 0.18–9.18) for PredictCBC-1A (**Table 5**); 1.33 (95% CI: 0.59–2.99, 95% PI: 0.14–12.76), 1.35 (95% CI: 0.65–2.77; 95% PI: 0.19–10.24) for PredictCBC-1B (**Table 5**)[5]. The calibration slope was close to 1 for CBCrisk (1.26, 95% CI: 1.01–1.50 and 95% PI: 1.01–1.50, **Table 3-5**), and PredictCBC-1A and 1B 0.90 (95% CI: 0.79–1.02; 95% PI: 0.73–1.08), and 0.81 (95% CI: 0.63–0.99; 95% PI: 0.50–1.12) (**Table 5**), while prognostic effects were far too large for the Manchester formula (slope: 0.39, 95% CI: 0.34–0.43, 95% PI: 0.34–0.43, **Table 4-5**). Calibration plots of CBCrisk at 5 and 10 years are shown in **Supplementary Figure 1** and **Supplementary Figure 2.** As reported previously[5], the AUCs at 5 and 10 years for PredictCBC-1A were 0.63 (95% CI: 0.58–0.67, 95% PI: 0.52–0.74), and 0.63 (95% CI: 0.59–0.66, 95% PI: 0.53–0.72), respectively; for PredictCBC-1B 0.59 (CI: 0.54–0.63, 95% PI: 0.46–0.71, **Table 5**), and 0.59 (95% CI: 0.56–0.62, 95% PI: 0.52–0.66, **Table 5**), respectively.

Table 2: Description of main patient and clinical factors used for evaluation of the models and formula ‡

Study* / Geographic area	Europe - other§	Europe - Scandinavia	Europe - United Kingdom	Netherlands - BOSOM	Netherlands - EMC	Netherlands - NCR	United States and Australia
N	15,183	12,928	11,921	3,760	3,390	83,138	2,436
Age at first diagnosis, *years* (%)							
<30	152 (1.0)	46 (0.4)	156 (1.3)	108 (2.9)	46 (1.4)	388 (0.5)	41 (1.7)
30-39	1,252 (8.2)	489 (3.8)	1,811 (15.2)	842 (22.4)	374 (11.0)	4,241 (5.1)	494 (20.3)
40+	13,779 (90.8)	12,393 (95.9)	9,954 (83.5)	2,810 (74.7)	2,970 (87.6)	78,509 (94.4)	1,901 (78.0)
Age at first birth = unknown (%)	15,183 (100.0)	12,928 (100.0)	11,921 (100.0)	3,760 (100.0)	3,390 (100.0)	83138 (100.0)	2,436 (100.0)
Family history (%)							
Yes	2,123 (14.0)	818 (6.3)	1,371 (11.5)	737 (19.6)	591 (17.4)	0 (0.0)	319 (13.1)
No	8,057 (53.1)	3,158 (24.4)	8,210 (68.9)	1,177 (31.3)	2,482 (73.2)	0 (0.0)	1,498 (61.5)
Unknown	5,003 (33.0)	8,952 (69.2)	2,340 (19.6)	1,846 (49.1)	317 (9.4)	83,138 (100.0)	619 (25.4)
First BC type = Pure invasive (%)	15,183 (100.0)	12,928 (100.0)	11,921 (100.0)	3,760 (100.0)	3,390 (100.0)	83,138 (100.0)	2,436 (100.0)
Breast density = unknown (%)	15,183 (100.0)	12,928 (100.0)	11,921 (100.0)	3,760 (100.0)	3,390 (100.0)	83,138 (100.0)	2,436 (100.0)
ER status (%)							
Negative	3,387 (22.3)	1,746 (13.5)	1,718 (14.4)	896 (23.8)	842 (24.8)	14,591 (17.6)	445 (18.3)
Positive	10,071 (66.3)	9,401 (72.7)	7,175 (60.2)	2,024 (53.8)	2,427 (71.6)	64,790 (77.9)	1,572 (64.5)
Unknown	1,725 (11.4)	1,781 (13.8)	3,028 (25.4)	840 (22.3)	121 (3.6)	3,757 (4.5)	419 (17.2)
High risk pre-neoplasia = unknown (%)	15,183 (100.0)	12,928 (100.0)	11,921 (100.0)	3,760 (100.0)	3,390 (100.0)	83,138 (100.0)	2,436 (100.0)
Anti-estrogen therapy (%)							
Yes	7,868 (51.8)	6,434 (49.8)	8,712 (73.1)	809 (21.5)	1,559 (46.0)	40,214 (48.4)	363 (14.9)
No	4,570 (30.1)	1,947 (15.1)	2,046 (17.2)	2,739 (72.8)	1,821 (53.7)	42,924 (51.6)	8 (0.3)
Unknown	2,745 (18.1)	4,547 (35.2)	1,163 (9.8)	212 (5.6)	10 (0.3)	0 (0.0)	2,065 (84.8)
CBC cumulative incidence (%)							
3-year (95% CI)	1.0 (0.8 - 1.2)	0.7 (0.5 - 0.9)	0.5 (0.3 - 0.7)	1.7 (1.3 - 2.1)	1.7 (1.2 - 2.1)	1.3 (1.2 - 1.4)	1.8 (0.8 - 2.8)
5-year (95% CI)	1.6 (1.4 - 1.9)	1.0 (0.8 - 1.3)	1.0 (0.8 - 1.3)	3.0 (2.5 - 3.6)	2.6 (2.1 - 3.2)	2.4 (2.3 - 2.5)	2.8 (1.7 - 3.8)
10-year (95% CI)	3.5 (3.1 - 3.9)	2.1 (1.7 - 2.4)	1.3 (1.0 - 1.5)	5.5 (4.7 - 6.2)	5.7 (4.9 - 6.6)	4.6 (4.5 - 4.8)	4.1 (3.0 - 5.3)

‡More details about the main patient and clinical characteristics by study are available in the supplementary information of [5]

Abbreviations:

* The studies denoted with Europe and United States and Australia are part of the Breast Cancer Association Consortium

§ Europe - other geographic area included studies from Belgium (1), Germany (2), Netherlands (2) and Poland (2).

BOSOM: Breast Cancer Outcome Study of Mutation carriers; EMC: Erasmus Medical Center; NCR: Netherlands Cancer Registry

BC: breast cancer; ER: estrogen receptor; CBC: contralateral breast cancer; CI: confidence interval;
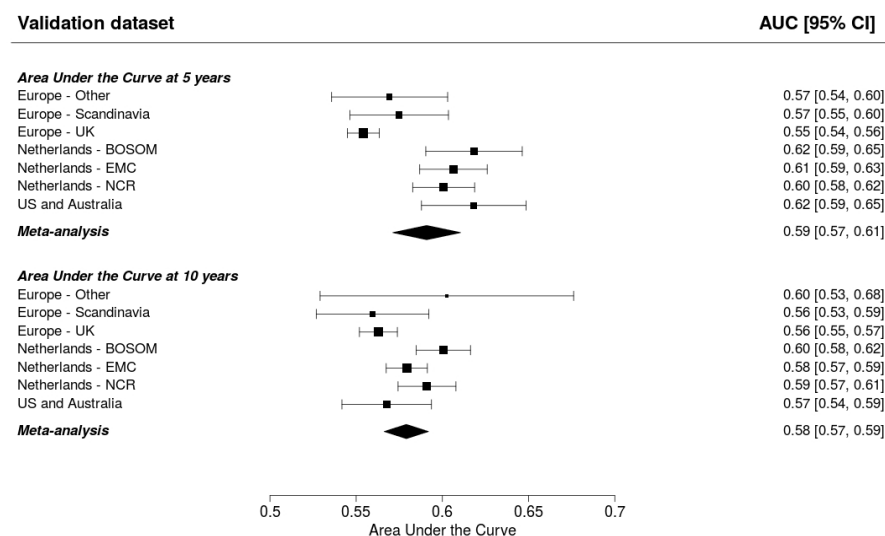
Validation dataset   **AUC [95% CI]**

Area Under the Curve at 5 years
Europe - Other   0.57 [0.54, 0.60]
Europe - Scandinavia   0.57 [0.55, 0.60]
Europe - UK   0.55 [0.54, 0.56]
Netherlands - BOSOM   0.62 [0.59, 0.65]
Netherlands - EMC   0.61 [0.59, 0.63]
Netherlands - NCR   0.60 [0.58, 0.62]
US and Australia   0.62 [0.59, 0.65]
Meta-analysis   0.59 [0.57, 0.61]

Area Under the Curve at 10 years
Europe - Other   0.60 [0.53, 0.68]
Europe - Scandinavia   0.56 [0.53, 0.59]
Europe - UK   0.56 [0.55, 0.57]
Netherlands - BOSOM   0.60 [0.58, 0.62]
Netherlands - EMC   0.58 [0.57, 0.59]
Netherlands - NCR   0.59 [0.57, 0.61]
US and Australia   0.57 [0.54, 0.59]
Meta-analysis   0.58 [0.57, 0.59]

Figure 1: Prediction performance of the CBCrisk model (Chowdhury et al. [7]). The upper and lower panel show the discrimination assessed by a time-dependent Area-Under-the-Curve at 5 and 10 years, respectively. The black squares indicate the estimated accuracy of a model built on 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 interval of the predictive accuracy.

Validation dataset   **AUC [95% CI]**

Area Under the Curve at 5 years
Europe - Other   0.60 [0.58, 0.63]
Europe - Scandinavia   0.56 [0.50, 0.61]
Europe - UK   0.62 [0.58, 0.67]
Netherlands - BOSOM   0.62 [0.60, 0.64]
Netherlands - EMC   0.61 [0.58, 0.64]
Netherlands - NCR   0.60 [0.57, 0.62]
US and Australia   0.62 [0.58, 0.66]
Meta-analysis   0.61 [0.60, 0.62]

Area Under the Curve at 10 years
Europe - Other   0.62 [0.58, 0.66]
Europe - Scandinavia   0.57 [0.53, 0.60]
Europe - UK   0.61 [0.58, 0.64]
Netherlands - BOSOM   0.61 [0.60, 0.62]
Netherlands - EMC   0.60 [0.56, 0.63]
Netherlands - NCR   0.60 [0.58, 0.61]
US and Australia   0.59 [0.56, 0.62]
Meta-analysis   0.60 [0.59, 0.61]
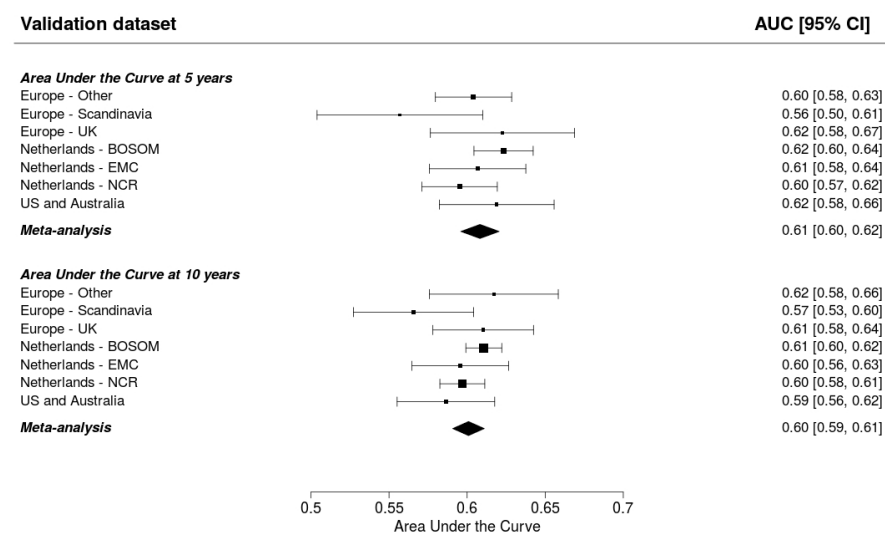
Figure 2: Prediction performance of the Manchester formula (Basu et al. [8]) The upper and lowerpanel show the discrimination assessed by a time-dependent Area-Under-the-Curve at 5 and 10 years, respectively. The black squares for each dataset indicate the estimated accuracy of a model built on all remaining studies or geographic areas. The black horizontal lines indicate the corresponding 95% confidence intervals of the estimated accuracy (intervalwhiskers). The black diamonds indicate the mean with the corresponding 95% confidence interval of the predictive accuracy.

Table 3: Calibration performance of the CBCrisk model[§]

Validation dataset	E/O ratio at 5 years (95% CI)	E/O ratio at 10 years (95% CI)	Calibration slope (95% CI)
Europe - Other	0.87 (076 - 0.98)	0.75 (0.68 - 0.81)	1.11 (0.40 - 1.83)
Europe - Scandinavia	1.59 (1.28 - 1.91)	1.23 (1.08 - 1.38)	0.86 (0.16 - 1.57)
Europe - UK	1.35 (1.38 - 2.17)	1.82 (1.53 - 2.11)	0.85 (-0.03 - 1.73)
Netherlands - BOSOM	0.45 (0.37 - 0.53)	0.50 (0.43 - 0.57)	1.34 (0.76 - 1.93)
Netherlands - EMC	0.48 (0.38 - 0.57)	0.43 (0.37 - 0.50)	1.19 (0.65 - 1.73)
Netherlands - NCR	0.57 (0.54 - 0.59)	0.54 (0.52 - 0.56)	1.40 (1.11 - 1.68)
US and Australia	0.43 (0.33 - 0.54)	0.56 (0.45 - 0.67)	1.13 (0.25 - 2.00)
Meta-analysis	0.86 (0.50 - 1.46)	0.82 (0.51 - 1.32)	1.26 (1.01 – 1.50)
95% PI	0.20 - 3.75	0.21 - 3.14	1.01 - 1.50

Abbreviations: E/O: expected-observed; CI: confidence interval; UK: United Kingdom; BOSOM: Breast Cancer Outcome Study of Mutation carriers; EMC: Erasmus Medical; Center NCR: Netherlands Cancer Registry; PI: prediction interval
[§]Chowdhury M, Euhus D, Onega T, Biswas S, Choudhary PK (2017) A model for individualized risk prediction of contralateral breast cancer. Breast Cancer Res Treat 161 (1):153-160.

Table 4: Calibration performance of the Manchester formula[§]

Validation dataset	E/O ratio at 5 years (95% CI)	E/O ratio at 10 years (95% CI)	Calibration slope (95% CI)
Europe - Other	1.64 (1.44 - 1.85)	1.46 (1.34 - 1.58)	0.40 (0.29 - 0.50)
Europe - Scandinavia	2.61 (2.09 - 3.12)	2.11 (1.85 - 2.37)	0.35 (0.13 - 0.57)
Europe - UK	3.34 (2.60 - 4.08)	3.49 (2.93 - 4.05)	0.42 (0.23 - 0.61)
Netherlands - BOSOM	0.81 (0.66 - 0.96)	0.92 (0.79 - 1.05)	0.45 (0.33 - 0.56)
Netherlands - EMC	0.94 (0.75 - 1.14)	0.87 (0.75 - 1.00)	0.35 (0.21 - 0.49)
Netherlands - NCR	1.00 (0.95 - 1.04)	1.01 (0.98 - 1.05)	0.37 (0.33 - 0.42)
US and Australia	0.77 (0.58 - 0.96)	1.02 (0.82 - 1.23)	0.51 (0.33 - 0.68)
Meta-analysis	1.54 (0.61 - 3.92)	1.53 (0.63 - 3.73)	0.39 (0.34 - 0.43)
95% PI	0.11 - 20.72	0.13 - 18.52	0.34 - 0.43

Abbreviations: E/O: expected-observed; CI: confidence interval; UK: United Kingdom; BOSOM: Breast Cancer Outcome Study of Mutation carriers; EMC: Erasmus Medical; Center NCR: Netherlands Cancer Registry; PI: prediction interval
[§]Basu NN, Ross GL, Evans DG, Barr L (2015) The Manchester guidelines for contralateral risk-reducing mastectomy. World J Surg Oncol 13:237

Sensitivity analysis showed that the performance measures of CBCrisk did not change when metachronous CBC was defined after 6 months since first BC diagnosis (see **Supplementary Materials, Supplementary Table 1-2 and Supplementary Figure 3**).

Table 5: Summary of prediction performance of CBCrisk, Manchester formula, and PredictCBC version 1A and version 1B with the corresponding 95% prediction intervals (PI).

Characteristics	CBCrisk§	Manchester formula†	PredictCBC version 1A‡*	PredictCBC version 1B‡*
Discrimination				
AUC at 5 years (95% PI)	0.59 (0.54 - 0.64)	0.61 (0.59 - 0.63)	0.63 (0.52 - 0.74)	0.59 (0.46 - 0.71)
AUC at 10 years (95% PI)	0.58 (0.55 - 0.61)	0.60 (0.58 - 0.62)	0.63 (0.53 - 0.72)	0.59 (0.52 - 0.66)
Calibration				
E/O ratio at 5 years (95% PI)	0.86 (0.20 - 3.75)	1.54 (0.11 - 20.72)	1.26 (0.14 - 11.34)	1.33 (0.14 - 12.76)
E/O ratio at 10 years (95% PI)	0.82 (0.21 - 3.14)	1.53 (0.13 - 18.52)	1.28 (0.18 - 9.18)	1.35 (0.19 - 10.24)
Slope (95% PI)	1.26 (1.01 - 1.50)	0.39 (0.34 - 0.43)	0.90 (0.73 - 1.08)	0.81 (0.50 - 1.12)

Abbreviations: AUC: Area under the curve; PI: prediction interval
§Chowdhury M, Euhus D, Onega T, Biswas S, Choudhary PK (2017) A model for individualized risk prediction of contralateral breast cancer. Breast Cancer Res Treat 161 (1):153-160.
†Basu NN, Ross GL, Evans DG, Barr L (2015) The Manchester guidelines for contralateral risk-reducing mastectomy. World J Surg Oncol 13:237
‡ Giardiello D, Steyerberg E, Hauptmann M, et al. (2019) Prediction and clinical utility of a contralateral breast cancer risk model. Breast Cancer Res. doi:10.1186/s13058-019-1221-1, Figure 1 and Figure S5
*version 1A includes *BRCA* mutation status as a variable while 1B does not.

DISCUSSION

Accurate CBC risk predictions are essential in clinical decision making around CPM or tailored surveillance among patients with first primary BC. In particular, overestimation of risk can lead to recommending CPM among BC patients with low risks. Underestimation can lead to suboptimal surveillance or hesitance about recommending CPM for patients with substantial risk. Using individual patient data from multiple studies with long follow-up, we externally evaluated the prediction performance accuracy of CBCrisk, a tool developed and validated to provide individualized CBC risk prediction, and the Manchester formula, a heuristically derived calculation of CBC lifetime risk[6,8,7,9]. In addition, the availability of different European-descendent studies allowed heterogeneity in the performance by geographic area to be assessed.

CBCrisk under-predicted the risk of CBC and had moderate discrimination ability with considerable heterogeneity between studies. The Manchester formula was empirically derived from a systematic review, and its discrimination accuracy was higher than CBCrisk. This may be explained by the inclusion of *BRCA1/2* mutation carrier information, an important determinant of CBC risk[21]. With the same large individual patient data sets, PredictCBC models had been developed and validated[5]. In particular, PredictCBC version 1A includes information of *BRCA1/2* mutation carriers and extensive information about the primary BC including treatments. The discrimination of all three prediction models was moderate, with AUC values around 0.6.

CBCrisk was previously externally validated using two independent clinical studies from Johns Hopkins University (JH) and MD Anderson Cancer Center (MDA) in the US[9]. Discrimination ability was 0.61 and 0.65 at 3 years, and 0.62 and 0.61 at 5 years for JH and MDA, respectively. The risk of CBC was overestimated in JH with E/O ratios of 2.02 and 1.56 at 3 and 5 years, while underestimated in MDA with E/O ratios of 0.61 and 0.62, respectively.

The considerable heterogeneity in all CBC risk calculators, especially in the CBCrisk and the Manchester formula, reflects the different CBC incidences in every study[13]. Another potential source of heterogeneity is the carrier frequency of germline mutations associated with CBC that may vary among studies, especially in the CBC calculators not including information of *BRCA1/2* mutation as CBCrisk and the PredictCBC-1B[22]. In addition, heterogeneity may be due to the different proportions of the use of (neo) adjuvant systemic therapies explained by the different distribution of tumor subtypes among studies[4]. Besides, inter-observer variation in pathological examination of BC among studies may lead to different adjuvant systemic therapy advice and, consequently, prediction of CBC risk[23]. Variation in prediction performance and limited generalizability of CBC risk calculators can also be partially explained by differences in how predictors are measured among studies[24,25]. For example, lack of family history knowledge may lead to uncertainty in risk prediction and varies according to demographics of the patients[26]. In particular, if in some studies BC patients misreported information about family history, the CBC risk would be over(under)estimated causing inappropriate decision-making regarding CPM or tailored surveillance. Some limitations of our study must be recognized. Firstly, our dataset, while large, had missing data for three covariates that were used in the CBCrisk model: breast density, age at first birth, and high risk preneoplasia. The authors of CBCrisk estimated the relative risks for patients with the unknown characteristics, but the use of the missing indicator variable is suboptimal compared to having the prognostic information available. It may lead to over or under-estimation of absolute CBC risk[27]. For this reason, we suggest that it is preferable to use multiple imputation of missing data, as is done in the PredictCBC models[28,29]. In addition, investigation of the potential source of model misspecification due to possible different definitions or measurement error was not possible[30-32].

In conclusion, current statistical risk prediction models and heuristic formulas provided moderate CBC individualized prediction performance. Careful re-calibration is required before considering these models for clinical decision making. A more direct comparison between the current CBC risk prediction models using a large external dataset with complete information on all factors included in all CBC prediction models would be ideal, but is currently unavailable. There is an ongoing debate about improvements of clinical prediction performance using machine learning approaches compared to

standard regression approaches for risk prediction[33,34]. However, irrespective of the methodology, better predictors are needed to predict CBC more accurately. Deeper biological insights and potential inclusion of other genetic markers such as *CHEK2* c.1100del mutation status and polygenic risk scores based on common genetic variants may improve CBC risk prediction, although rare mutations are unlikely to contribute substantially to CBC risk in the general population[35,36]. Life-style factors such as body mass index, alcohol consumption, and smoking also may help to better stratify high and low CBC risk patients even though these factors are difficult to measure accurately. Moreover, breast density may be important. More detailed information about adjuvant systemic therapies may better identify patients with low and high CBC risk since chemotherapy and especially endocrine therapy reduce CBC risk[4]. After extension and further external validation of prediction models for CBC risk, investigation of their potential clinical utility is an important future step.

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SUPPLEMENTARY MATERIAL

1. From Manchester guidelines to Manchester formula

A simple formula has been proposed by Basu et al. to calculate the life-time risk of contralateral breast cancer (CBC) based on a literature review of risk factors. We translated the life-time risk to 5- and 10-year CBC risk to compare the prediction performance with CBCrisk and PredictCBC. A complete overview is given in the following schema:

Manchester guidelines (life-time CBC risk)	Manchester formula (CBC risk at 5 and 10 years)
Step 1: calculate the number of years of CBC risk using 80 years as the average life expectancy. The number of years of CBC risk (N) can be calculated as:	**Step 1:** set CBC risk at 5 and 10 years assuming the number of years at risk of CBC (N) be 5 and 10, respectively:
$N = 80\ \text{years} - \text{patient age (years)}$	$N = 5\ \text{or}\ 10$
Step 2: calculate the life-time risk (L) using the annual incidence of CBC at 0.5% among patients diagnosed with first invasive breast cancer:	**Step 2:** calculate the CBC risk at 5 and 10 years using an annual incidence of CBC of 0.5% among patients diagnosed with first invasive breast cancer:
$L = N \times 0.5\%$	$L = 5 \times 0.5\%$ (5-year CBC risk) $L = 10 \times 0.5\%$ (10-year CBC risk)
Step 3: The life-time risk can be modified based on patient's personal risk profile as: • For patients with estrogen-receptor positive disease: $L \times 0.5$; • For patients with a *BRCA1/2* germline mutation*: $L \times 4$; • For patients with oophorectomy under age of 40 years: $L \times 0.5$ • For patients with a family history of breast cancer*: $L \times 2$; * For patients with a *BRCA1/2* germline mutation and a family history: $L \times 4$.	**Step 3:** according to the information of the risk factors available, calculate the 5- and 10-year CBC personalized risk (Y): $Y = L \times (1\text{-}0.5X_1) \times (1\text{-}0.5X_2) \times (1+X_3+3X_4 - X_5)]$ Where: $X_1 = 1$ (if estrogen-receptor positive, 0 else) $X_2 = 1$ (if oophorectomy under 40 years, 0 else) $X_3 = 1$ (if family history, 0 else) $X_4 = 1$ (if BRCA mutation, 0 else) $X5 = 1$ (if BRCA mutation and family history, 0 else)

2. Sensitivity analysis

The PredictCBC and CBCrisk models considered contralateral breast cancer (CBC) more than 3 and 6 months after the first invasive breast cancer (BC) diagnosis as metachronous, respectively. A sensitivity analysis was done to evaluate the performance of CBCrisk by

considering metachronous CBC after 6 months since first BC. Discrimination accuracy at 5 years was 0.59 with the corresponding 95% confidence interval (CI) between 0.57 and 0.61 (**Supplementary Figure 3**), and the corresponding 95% prediction interval (PI) between 0.54 and 0.64. Discrimination accuracy at 10 years was 0.58 (95% CI: 0.57–0.59; 95% PI: 0.55–0.61, **Supplementary Figure 3**). The expected/observed (E/O) ratio at 5 years was 0.89 (95% CI:0.53–1.49.; 95% PI: 0.21–3.72) and at 10 years was 0.84 (95% CI: 0.53–1.34; 95% PI: 0.23–3.13) (**Supplementary Table 1**). The calibration slope was 1.26 (95% CI: 1.01–1.51; 95% PI: 1.01–1.51). An overview of prediction performances of the main results and those from the sensitivity analysis are shown in **Supplementary Table 2**.

Supplementary Figure 1: Calibration plot of CBCrisk at 5 years
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.

Supplementary Table 1: Calibration performances of CBCrisk from the sensitivity analysis defining CBC as an event 6 months after the first breast cancer diagnosis
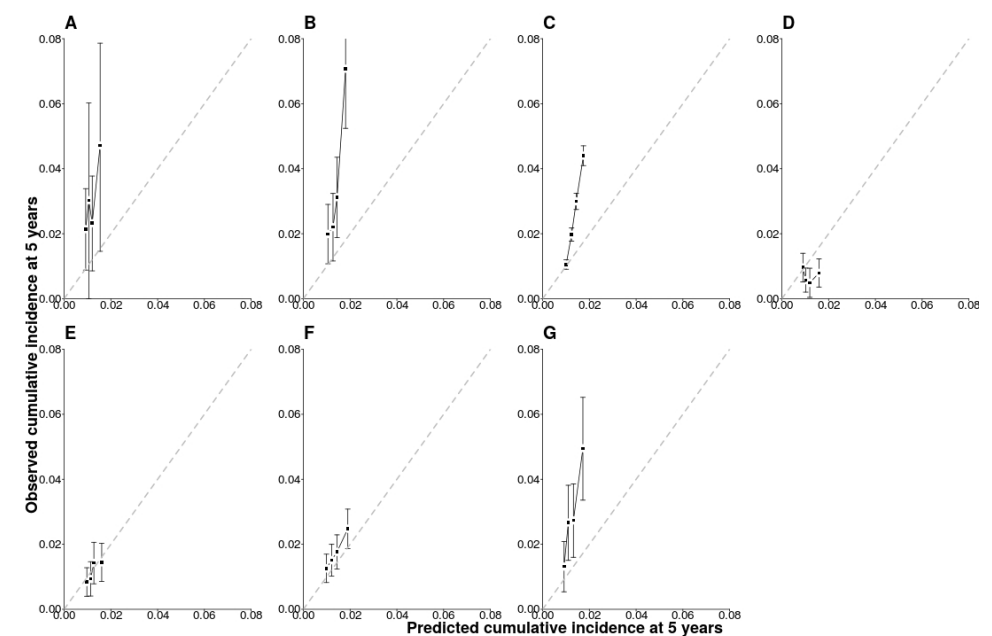
Validation dataset	E/O ratio at 5 years (95% CI)	E/O ratio at 10 years (95% CI)	Calibration slope (95% CI)
Europe - Other	0.92 (0.80 - 1.04)	0.76 (0.69 - 0.83)	1.17 (0.44 - 1.91)
Europe - Scandinavia	1.61 (1.29 - 1.93)	1.24 (1.08 - 1.39)	0.84 (0.14 -1.55)
Europe - UK	1.77 (1.38 - 2.17)	1.82 (1.53 - 2.11)	0.85 (-0.03 - 1.73)
Netherlands - BOSOM	0.47 (0.38 - 0.56)	0.51 (0.44 - 0.58)	1.33 (0.73 - 1.92)
Netherlands - EMC	0.49 (0.39 - 0.59)	0.44 (0.38 - 0.50)	1.22 (0.68 - 1.77)
Netherlands - NCR	0.58 (0.55 - 0.61)	0.55 (0.53 - 0.56)	1.40 (1.11 - 1.69)
US and Australia	0.56 (0.40 - 0.72)	0.66 (0.52 - 0.80)	1.15 (0.27 - 2.03)
Meta-analysis	0.89 (0.53 - 1.49)	0.84 (0.53 - 1.34)	1.26 (1.01 - 1.51)
95% PI	0.21 - 3.72	0.23 - 3.13	1.01 - 1.51

Abbreviations: E/O: expected/observed; PI: prediction interval;
BOSOM: Breast Cancer Outcome Study of Mutation carriers; EMC: Erasmus Medical Center; UK: United Kingdom;
NCR: Netherlands Cancer Registry

Supplementary Table 2: An overview of prediction performances of the CBCrisk model
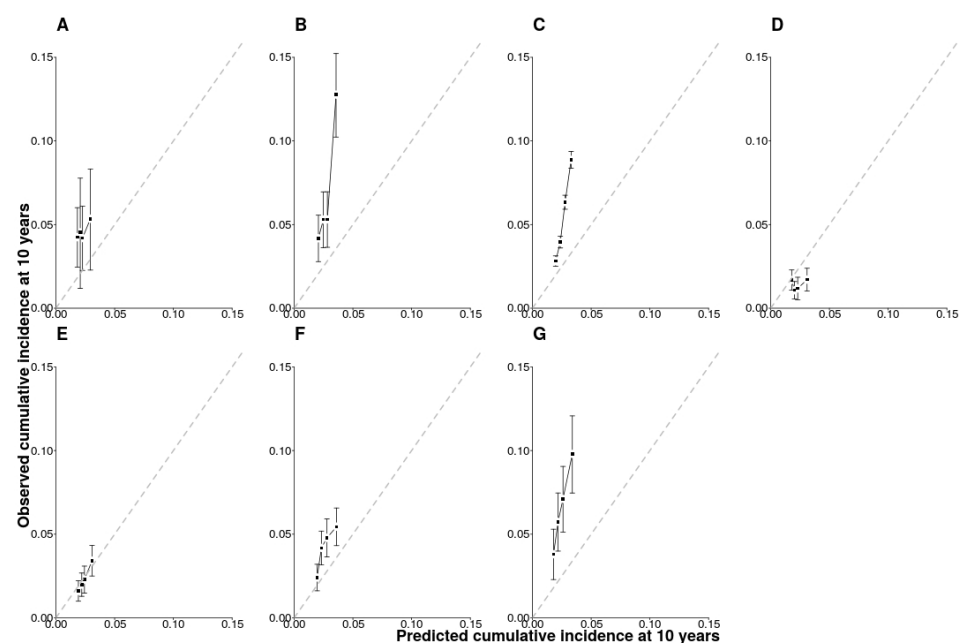
Characteristics	CBCrisk CBC definition 3 months	CBCrisk CBC definition 6 months (sensitivity analysis)
Discrimination		
AUC at 5 years (95% PI)	0.59 (0.54–0.64)	0.59 (0.54–0.64)
AUC at 10 years (95% PI)	0.58 (0.55–0.61)	0.58 (0.55–0.61)
Calibration		
E/O ratio at 5 years (95% PI)	0.86 (0.20–3.75)	0.89 (0.21–3.72)
E/O ratio at 10 years (95% PI)	0.82 (0.27–2.51)	0.84 (0.23–3.13)
Slope (95% PI)	1.26 (1.01–1.50)	1.26 (1.01–1.51)

Abbreviations:
AUC: Area-Under-the-Curve;
PI: prediction interval
E/O: expected/observed

Supplementary Figure 2: Calibration plot of CBCrisk at 10 years

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.
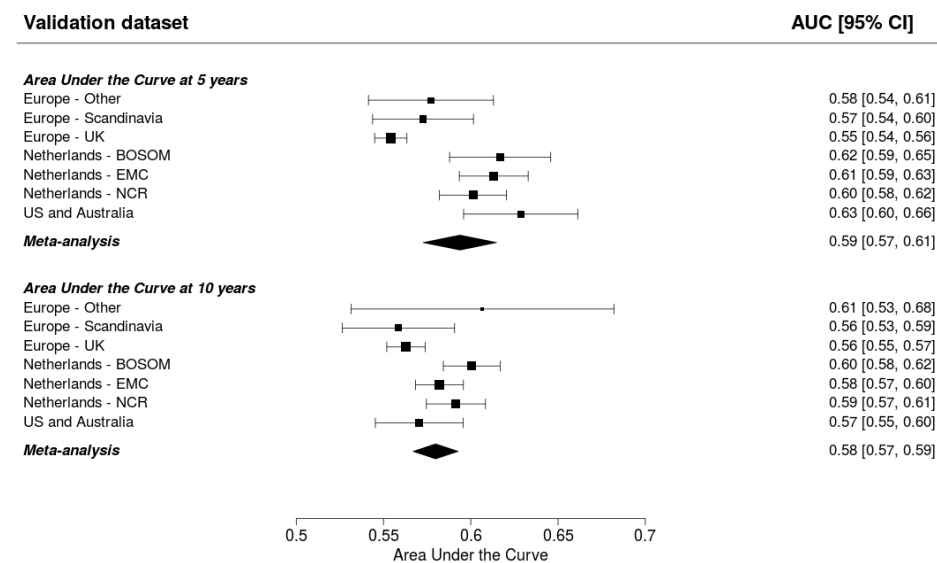
Supplementary Figure 3: Sensitivity analysis of CBCrisk prediction performances. A metachronous contralateral breast cancer was defined after 6 months since the first breast cancer diagnosis. The upper and lower panel show the discrimination assessed by a time-dependent Area-Under-the-Curve at 5 and 10 years, respectively. The black squares for each dataset indicate the estimated accuracy of a model built on 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 interval of the predictive accuracy.