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Breast cancer polygenic risk score and contralateral breast cancer risk

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1 **Abstract**

2 Previous research has shown that polygenic risk scores (PRS) can be used to stratify women
3 according to their risk of developing primary invasive breast cancer. This study aimed to
4 evaluate the association between a recently validated PRS of 313 germline variants (PRS₃₁₃)
5 and contralateral breast cancer (CBC) risk. We included 56,068 women of European ancestry
6 diagnosed with first invasive breast cancer from 1990 onwards with follow-up from the Breast
7 Cancer Association Consortium. Metachronous CBC risk (N=1,027) according to the distribution
8 of the PRS₃₁₃ was quantified using Cox regression analyses. We assessed PRS₃₁₃ interaction
9 with age at first diagnosis, family history, morphology, ER-, PR-, and HER2-status, and
10 (neo)adjuvant therapy. In Asian studies, with limited follow-up, CBC risk associated with PRS₃₁₃
11 was assessed using logistic regression for 340 women with CBC compared with 12,133 women
12 with unilateral breast cancer. Higher PRS₃₁₃ was associated with increased CBC risk: hazard
13 ratio per standard deviation (SD)=1.25 (95%CI=1.18-1.33) for Europeans, and an OR per
14 SD=1.15 (95%CI=1.02-1.29) for Asians. The absolute lifetime risks of CBC, accounting for
15 death as competing risk, were 12.4% for European women at the 10th percentile and 20.5% at
16 the 90th percentile of the PRS₃₁₃. We found no evidence of confounding by, or interaction with
17 patient characteristics, characteristics of the primary tumor, or treatment. The C-index for the
18 PRS₃₁₃ alone was 0.563 (95%CI=0.547-0.586). In conclusion, the PRS₃₁₃ is an independent
19 factor associated with CBC risk, and may be incorporated in CBC risk prediction models to help
20 improve stratification of patients and optimize surveillance and treatment strategies.

21 **Introduction**

22 Due to the high incidence of breast cancer and improving survival, an increasing number of
23 breast cancer survivors are at risk of developing contralateral breast cancer (CBC). The 10-year
24 cumulative incidence of CBC is ~4%^{1, 2}, however estimates vary widely depending on factors
25 such as germline genetics, family history, and (neo)adjuvant systemic therapy for the first breast
26 cancer³. The risk of developing CBC is particularly high in women carrying rare mutations in
27 certain genes including *BRCA1*, *BRCA2*, and *CHEK2*, with approximately two- to fourfold higher
28 risks reported compared with non-carriers³.

29
30 Recently, genome-wide association studies (GWAS) have identified multiple common germline
31 variants that are associated with first primary breast cancer risk^{4, 5}. These are associated with
32 small differences in risk individually, but their combined effects can be summarized in a
33 polygenic risk score (PRS), which has been shown to stratify women according to their risk of
34 developing breast cancer⁶⁻⁹. Using a large GWAS dataset from the Breast Cancer Association
35 Consortium (BCAC), we previously developed and validated a 313-variant PRS (PRS₃₁₃) among
36 women of European descent. In independent prospective studies, this PRS₃₁₃ predicted the risk
37 of primary invasive breast cancer with an odds ratio (OR) per standard deviation (SD) of 1.61
38 (95% confidence interval (95%CI)=1.57-1.65)⁷. The PRS₃₁₃ has also been externally validated
39 using the UK Biobank cohort.

40
41 The aim of the current study was to evaluate the association between PRS₃₁₃ and CBC risk,
42 using data from BCAC. Other studies have shown associations between risk of CBC and both a
43 67-variant PRS¹⁰ and individual variants¹¹, but not yet with PRS₃₁₃, the most extensively
44 validated PRS. Further, the data-set currently evaluated is larger than those previously tested.
45 We carried out two types of analyses. We conducted a cohort study among studies of European
46 ancestry women with follow-up data available, and performed Cox regression analyses to

47 estimate hazard ratios (HRs) for CBC. Potential confounding and interaction with patient
48 characteristics, characteristics of the primary tumor, or treatment were tested. In addition, to
49 directly compare the OR reported for PRS₃₁₃ and first breast cancer, we selected case-case
50 series and performed logistic regression analyses comparing the PRS₃₁₃ distribution in women
51 with CBC versus those with unilateral breast cancer. These analyses were conducted
52 separately in European and Asian women (follow-up was too limited to perform a cohort study
53 for the Asian population).

54 **Material and Methods**

55 **Study subjects**

56 *Case-case series*

57 We selected women who were diagnosed with breast cancer and women without any diagnosis
58 of breast cancer from the BCAC including all women of European ancestry, based on
59 genotyping data, selecting only those studies which reported on CBC (62 studies) (Figure S1A,
60 Table S1-S2). BCAC database version freeze 12 was used. All women diagnosed with invasive
61 breast cancer as a first cancer were included in the analysis; the small number of tumors with
62 unknown invasiveness were considered invasive (Table S2). In the case-case series, a CBC
63 was defined as a breast cancer (in situ or invasive) in the contralateral breast irrespective of the
64 time since the first breast cancer. The case-case series comprised 81,000 women with
65 unilateral breast cancer, 3,607 women with CBC, and 62,830 women without any diagnosis of
66 breast cancer (Figure S1A). We also compared unilateral breast cancers to women without any
67 diagnosis of breast cancer to reproduce earlier published estimates⁷ in our set of studies with
68 information available on CBC.

69

70 We selected for a separate analysis women of Asian ancestry of the BCAC data comprising
71 12,133 women with unilateral breast cancer, 340 women with CBC, and 13,398 women without
72 any diagnosis of breast cancer from eight studies (Figure S1B, Table S2).

73

74 *Cohort*

75 In the cohort we used metachronous CBC as the outcome, defined as a breast cancer in the
76 contralateral breast (in situ or invasive) diagnosed at least three months after the first breast
77 cancer. We used a cut-off of three months to increase the likelihood that these CBCs represent
78 true second primary tumors rather than metastases or synchronous bilateral tumors. We
79 selected all women diagnosed with breast cancer from the European case-case series and

80 excluded four studies that did not provide follow-up information on vital status (Figure S1A). We
81 did not include Asian women since follow-up was too limited in these studies. We additionally
82 excluded 6,207 women with no follow-up and 2,208 women who developed synchronous CBC,
83 distant metastasis, or who died or last known to be alive within three months after the first
84 breast cancer diagnosis. Since BCAC also included prevalent cases, we excluded 3,796 women
85 who developed CBC or were censored before study entry. The case-case series included
86 women diagnosed between 1947 and 2018. In the cohort, we excluded 2,235 women who were
87 diagnosed with their first breast cancer before 1990 or who had missing year of first diagnosis.
88 We restricted to women diagnosed from 1990 onwards so that diagnostic procedures and
89 treatment would be more representative of current practice. Moreover, clinico-pathological,
90 treatment and follow-up data were more complete after 1990. In addition, we excluded 16
91 studies (9,783 women) without information about metachronous CBC events (Figure S1A). After
92 these exclusions, the cohort for this analysis comprised data from 42 studies, including 56,068
93 women with invasive breast cancer among whom 1,027 metachronous CBC occurred (Table
94 S2).

95

96 All individuals provided written informed consent, and all studies were approved by the relevant
97 institutional review boards. BCAC data were centrally harmonized and cleaned in
98 communication with the study data managers and principal investigators. Data collection for
99 individual studies is described in Table S1.

100

101 *UK biobank cohort*

102 We performed a secondary analysis of the association between the overall breast cancer
103 PRS₃₁₃ and risk of second breast cancer among 10,567 women in the UK biobank cohort. For
104 details see Supplement UK biobank.

105

106 **Genotyping and PRS**

107 DNA samples from participants were genotyped using the iCOGS array^{12; 13} or the OncoArray^{4;}
108 ¹⁴, with genotypes for variants not on the arrays estimated by imputation^{4; 13}. The PRS₃₁₃ was
109 calculated as a weighted sum of the minor allele dosages; the variant selection and weights are
110 as given by Mavaddat et al.⁷. We also calculated estimates for a previously published PRS₇₇⁶,
111 and estrogen receptor (ER)-specific PRSs (ER-positive PRS₃₁₃ and ER-negative PRS₃₁₃)⁷. The
112 ER-specific PRSs were constructed by defining subtype-specific weights for the 313 variants
113 using a hybrid approach⁷. Variants and corresponding coefficients used to construct the PRS
114 are shown in Table S3. We standardized the PRS in our analyses by dividing it by the SD of the
115 PRS of the controls (PRS₇₇ SD=0.45; PRS₃₁₃ SD=0.61; ER-positive PRS₃₁₃ SD=0.65; ER-
116 negative PRS₃₁₃ SD=0.59) exactly as was done in the analyses of the PRS and first breast
117 cancer risk^{6; 7}. This allows a direct comparison of the magnitude of the CBC relative risk
118 estimation to that of the first breast cancer.

119
120 For samples genotyped with both OncoArray and iCOGS array (9,071 samples), OncoArray
121 data were used in preference as the imputation quality was generally higher. The intraclass
122 correlation coefficient (ICC) between the PRS derived from the two platforms was 0.99
123 (95%CI=0.99-0.99) for the PRS₇₇, and 0.96 (95%CI=0.95-0.96) for PRS₃₁₃ (Figure S2). Given
124 the high correlation between the two platforms, PRS measures from both platforms were used
125 in the analyses without adjustment.

126 127 **Statistical analysis**

128 *Cohort*

129 The primary outcome in the cohort was the development of metachronous CBC. Cox
130 proportional hazards models were used to estimate HRs for metachronous CBC risk by PRS,
131 stratified by country. Since previous studies have shown that age at first breast cancer

132 diagnosis is an important predictor of CBC³, the analyses were performed with attained age as
133 the time scale. Time at risk started three months after the first breast cancer diagnosis and
134 ended at the age of CBC diagnosis, distant metastasis (where available), death, or end of
135 follow-up, whichever came first. For patients that had a study entry more than three months
136 after first breast cancer diagnosis, follow-up started at the age of study entry. We also
137 performed a fixed-effect meta-analysis of country-specific effects using the STATA command
138 *metan*. We performed a fixed-effect meta-analysis over a random-effect meta-analysis since
139 there was no evidence for heterogeneity in effect sizes between countries (I-squared=0%,
140 Figure S3). For some analyses, only invasive CBC was used as the outcome; in these analyses
141 we censored on in situ CBC. Separate analyses were conducted for ER-positive CBC (censored
142 on ER-negative- and ER-unknown CBC) and ER-negative CBC (censored on ER-positive- and
143 ER-unknown CBC).

144
145 We evaluated the linearity of the association between PRS₃₁₃ per unit SD and CBC risk using
146 restricted cubic splines with three knots. There was no evidence for violation of the linearity
147 assumption. Therefore, in the main analysis, the PRS₃₁₃ was treated as a continuous covariate,
148 and estimated the HR per unit SD of the PRS₃₁₃. Violation of the proportional hazard assumption
149 was assessed by inspection of the Schoenfeld residuals¹⁵. As a second analysis, we used the
150 per SD log HR of the PRS₃₁₃ to calculate the predicted HR at different percentiles of the PRS₃₁₃,
151 compared to the 50th percentile. Third, the PRS₃₁₃ was categorized into percentile groups (0th to
152 10th, 10th to 20th, 20th to 40th, 40th to 60th, 60th to 80th, 80th to 90th, 90th to 100th) to illustrate the
153 differences between PRS₃₁₃ subgroups, with the middle quintile (40th to 60th) as the reference.

154
155 We also performed multivariable Cox regression analyses to determine whether the log HR of
156 CBC risk by PRS changed when adjusting for year of first breast cancer diagnosis, family
157 history of breast cancer in a first degree relative, and several clinical characteristics of the first

158 breast cancer such as nodal status, tumor size, morphology, ER-, progesterone receptor (PR)-
159 and human epidermal growth factor receptor 2 (HER2)-status, (neo)adjuvant chemotherapy,
160 adjuvant endocrine therapy, and radiotherapy. These analyses were performed in all patients, a
161 complete case set (excluding patients with unknown values for the covariates), and in a set
162 excluding studies oversampling cases with family history. Potential effect modification of the
163 PRS₃₁₃ effect by the same variables was evaluated by fitting interaction terms in different
164 models using complete case sets, including the standardized PRS₃₁₃, modifier, and interaction.

165
166 The discriminative ability of different models; ([model 1] PRS₃₁₃ alone, [model 2] other risk
167 factors (the adjustment variables from the multivariable Cox regression analyses), [model 3]
168 PRS₃₁₃ + other risk factors) was calculated using Harrell's C-index¹⁶. Since no standard
169 performance measures are currently available to account for left-truncated follow-up time (*i.e.*,
170 to start analyses at age at study entry), we used time since first breast cancer as the time scale
171 to calculate the C-index.

172 173 *Absolute risks*

174 We followed the procedure as previously described¹⁷. Absolute risks of developing CBC at
175 PRS₃₁₃ percentiles were calculated using the estimated log HRs per SD from the breast cancer
176 cohort (BCAC) under the log-linear model, assuming the PRS is normally distributed. The
177 PRS₃₁₃- and age-specific incidences were constrained to the age-specific CBC incidences from
178 women diagnosed with a first invasive breast cancer in the period 2003-2010 from the
179 Netherlands Cancer Registry (NCR)¹. The age-specific CBC incidences were calculated overall
180 and for age-specific groups, censoring on death and distant metastasis. We used data from the
181 NCR since this registry has complete coverage of all newly diagnosed cancers in the
182 Netherlands. The NCR cohort included all females aged ≥ 18 years and follow-up for second
183 cancers was complete until February 1, 2016¹. We then applied the competing risk of dying on

184 the absolute CBC risks. The absolute CBC risk (AR_g) by age t in PRS₃₁₃ category g , taking into
185 account the competing risk of dying was calculated by:

186

$$AR_g(t) = \sum_{u=0}^{t-1} \mu_g(u)S_g(u)S_m(u)$$

187 Where $\mu_g(t)$ is the CBC incidence associated with PRS₃₁₃ category g , $S_g(t)$ the probability of
188 being free of CBC to age t , and $S_m(t)$ the probability of surviving to age t .

189

190 *Case-case series*

191 For the case-case series (European and Asian), logistic regression models were used to
192 estimate the ORs for CBC risk (comparing with unilateral breast cancer) and for unilateral breast
193 cancer risk (comparing with women without any diagnosis of breast cancer) associated with
194 PRS₃₁₃. All analyses were adjusted for age and country (Table S1). For all unilateral- and
195 contralateral breast cancer patients we used age at first breast cancer diagnosis, and for
196 women without any diagnosis of breast cancer we used age at baseline questionnaire.

197

198 For direct comparison with the estimate reported for PRS₃₁₃ and first breast cancer, we also
199 performed logistic regression analyses in the same BCAC study participants included in the
200 validation of the association between PRS₃₁₃ and first breast cancer risk⁷. This validation set
201 comprised a subsample from 24 studies and included 3,781 women with unilateral breast
202 cancer, 94 women with CBC, and 3,753 women without any diagnosis of breast cancer (Table
203 S2). For this analysis, we adjusted for 10 principal components, in line with Mavaddat et al.⁷.

204

205 For European women who had follow-up time available more than three months after the first
206 breast cancer diagnosis, a sensitivity analysis was performed for metachronous CBC (1,702
207 CBCs). We also did a separate analysis for invasive CBC (N=3,246), by excluding CBC in situ.

208

209 All P-values are two sided; tests with $P < .05$ are referred to as statistically significant. Analyses
210 were performed using STATA, version 13.1 (StataCorp) and R version 3.3.2.

211 **Results**

212 *European (cohort) Cox regression analyses*

213 The cohort included 56,068 women diagnosed with first invasive breast cancer with 1,027
214 metachronous CBC events. Median follow-up was 8.4 years. Patient, tumor, and treatment
215 characteristics are summarized in Table S4.

216

217 The associations between the different PRSs and CBC risk are shown in Table 1. The HR for
218 CBC per SD of PRS₃₁₃ was 1.25 (95%CI=1.18-1.33). For comparison, the HR per SD for PRS₇₇
219 was 1.21 (95%CI=1.14-1.29). Women within the 0th to 10th and the 90th to 100th percentile of the
220 PRS₃₁₃ had 0.59-fold (95%CI=0.45-0.78) and 1.38-fold (95%CI=1.13-1.69) risks of CBC,
221 respectively, compared with women within the 40th to 60th percentile (Figure 1, Table S5). The
222 predicted HRs of CBC for women at the 10th and 90th percentile of the PRS₃₁₃ were 0.75 and
223 1.33, respectively, compared to the 50th percentile (Figure 1). Since we observed evidence of
224 departure from the proportional hazards assumption ($P=0.02$)¹⁵, we also calculated HRs
225 stratified for follow-up duration (<five and ≥five years). The HR by SD of the PRS₃₁₃ was 1.21
226 (95%CI=1.10-1.32) for CBC diagnosed ≤five years after first breast cancer diagnosis (CBC
227 N=428), and 1.28 (95%CI=1.18-1.38) for CBC diagnosed >five years after first diagnosis (CBC
228 N=599).

229

230 The HR per SD of PRS₃₁₃ for ER-positive invasive CBC was 1.38 (95%CI=1.23-1.55), compared
231 to a HR per SD of the ER-positive PRS₃₁₃ of 1.37 (95%CI=1.22-1.54) (Table 1). For ER-negative
232 invasive CBC, the HR per SD was 0.92 (95%CI=0.75-1.12) for PRS₃₁₃ and 1.06 (95%CI=0.86-
233 1.30) for the ER-negative PRS₃₁₃.

234

235 Sensitivity analysis using the overall PRS₃₁₃ showed a HR per SD of 1.24 (95%CI=1.16-1.32) for
236 invasive CBC risk. When we used time since first breast cancer as the time scale, we found

237 similar results (HR per SD=1.25, 95%CI=1.18-1.33). Meta-analysis of country-specific effects
238 showed a HR per SD of 1.25 (95%CI=1.18-1.33) for CBC risk by PRS₃₁₃ (Figure S3).

239
240 The association between the PRS₃₁₃ and CBC risk did not change when adjusting for patient,
241 tumor, and treatment characteristics, nor when excluding studies oversampling cases with a
242 family history (Table S6). When considering potential modifiers of the effect of the PRS₃₁₃ on
243 CBC risk (Table 2), we found that the HR was the lowest in women aged <40 years at first
244 breast cancer diagnosis (HR per SD=1.13; 95%CI=0.98-1.31), and tended to increase with age,
245 although these effects were not statistically significant ($P_{\text{heterogeneity}}=.26$; $P_{\text{trend}}=.05$). We found no
246 indication for effect modification by family history ($P_{\text{heterogeneity}}=.63$), morphology ($P_{\text{heterogeneity}}=.14$),
247 ER-status ($P_{\text{heterogeneity}}=.13$), PR-status ($P=.26$), HER2-status ($P_{\text{heterogeneity}}=.42$), chemotherapy
248 ($P_{\text{heterogeneity}}=.60$), endocrine therapy ($P_{\text{heterogeneity}}=.79$), or radiotherapy ($P_{\text{heterogeneity}}=.40$) (Table
249 2).

250
251 The C-index was 0.563 (95%CI=0.547-0.586) for the model only including PRS₃₁₃, 0.605
252 (95%CI=0.591-0.629) for the model only including other risk factors, and 0.623 (95%CI=0.608-
253 0.645) for the complete model (Table 3).

254 255 *Absolute risks*

256 Based on the HR estimates for PRS₃₁₃, the predicted CBC risk by age 80 years was 12.4% at
257 the 10th percentile of the PRS₃₁₃, compared with 20.5% at the 90th percentile of the PRS₃₁₃
258 (Figure 2), accounting for death as competing risk. When death was not taken into account as
259 competing risk, the corresponding predicted risks by age 80 were 17.0% at the 10th percentile
260 and 27.9% at the 90th percentile of the PRS₃₁₃ (Figure S4). Table 4 shows the five- and 10-year
261 cumulative CBC risks by PRS₃₁₃ for different age groups, accounting for death as competing risk
262 (Table S7 shows results without competing risks).

263 *European and Asian (case-case series) logistic regression analyses*

264 Figure 3 shows the distribution of the PRS₃₁₃ per SD in the European case-case series. Median
265 PRS₃₁₃ was -0.4 (interquartile range [IQR]=1.35) for control women without any diagnosis of
266 breast cancer (N=81,000), 0.2 (IQR=1.36) for women with unilateral breast cancer (N=62,830),
267 and 0.5 (IQR=1.40) for women with CBC (N=3,607). The OR for unilateral breast cancer per SD
268 of the PRS₃₁₃ was 1.82 (95%CI=1.80-1.84) compared to control women (Table S8). The OR for
269 CBC per SD of PRS₃₁₃ was 1.30 (95%CI=1.26-1.35) compared to unilateral breast cancer.

270

271 In sensitivity analyses, the OR per SD of PRS₃₁₃ was 1.27 (95%CI=1.21-1.33) for metachronous
272 CBC and the OR per SD was 1.29 (95%CI=1.24-1.33) for invasive CBC, compared to unilateral
273 breast cancer. When analyses were restricted to the validation set of Mavaddat et al⁷, the OR
274 for unilateral breast cancer per SD of the PRS₃₁₃ was 1.67 (95%CI=1.59-1.76) compared to
275 control women, and the OR for CBC per SD of PRS₃₁₃ was 1.39 (95%CI=1.13-1.70) compared
276 to unilateral breast cancer (Table S8).

277

278 For women of Asian descent, the OR for unilateral breast cancer per SD of the PRS₃₁₃ was 1.56
279 (95%CI=1.52-1.60) compared to control women, and the OR for CBC per SD of PRS₃₁₃ was
280 1.15 (95%CI=1.02-1.29) compared to women with unilateral breast cancer (Table S8).

281 **Discussion**

282 Previous studies have shown that a PRS, summarizing the effects of common germline
283 variants, can be used to stratify women with respect to their risk to develop a primary breast
284 cancer⁶⁻⁹. In this study, we observed a clear association between the PRS₃₁₃ and CBC risk in
285 women of both European and Asian ancestry. The association was observed in both the case-
286 case series and the cohort. The HRs per SD of CBC for women at the 10th and 90th percentile of
287 the continuous predicted PRS₃₁₃ were 0.75 and 1.33, respectively, compared to the 50th
288 percentile. This translates to absolute risks at the 10th and the 90th percentile of the PRS₃₁₃ of
289 12.4% and 20.5%, respectively, by age 80 years. We estimated a C-index for the PRS₃₁₃,
290 summarizing its discriminatory ability, of 0.563 in the European cohort.

291
292 One previous study has investigated the effect of a PRS, including 67 variants, and CBC risk¹⁰.
293 This study found a risk ratio of 1.75 (95%CI=1.41-2.18) for women in the upper quartile of the
294 PRS compared with women in the lowest quartile. To facilitate comparison, we performed a
295 similar analysis in our case-case series, showing an OR of 1.98 (95%CI=1.79-2.18), adjusted
296 for country and age at first diagnosis, for women in the upper quartile of the PRS₃₁₃. This
297 indicates the PRS₃₁₃ improves stratification relative to PRSs including fewer variants. Moreover,
298 in our cohort, the C-index for the PRS alone improved from 0.547 (95%CI=0.536-0.575) for the
299 previously reported PRS₇₇⁶ to 0.563 (95%CI=0.547-0.586) for the PRS₃₁₃.

300
301 We found no evidence that the association between the PRS₃₁₃ and CBC risk was confounded
302 by family history, adjuvant therapy, morphology, age, or tumor receptor status of the first breast
303 cancer, nor that there was effect modification by those factors. The absence of notable effect
304 modification is in line with the abovementioned study of a 67-variant PRS and CBC risk; no
305 heterogeneity in association was found by age, family history, morphology, ER-status, and
306 adjuvant treatment¹⁰.

307

308 We considered the UK biobank cohort the most logical choice, given the large number of
309 women diagnosed with breast cancer with information available on the PRS₃₁₃, for an external
310 validation of our findings. However, it became apparent that the UK biobank cohort had no
311 information available on the laterality of the tumor. Therefore, it was not possible to distinguish
312 between contralateral and ipsilateral breast cancers and we performed analyses using any
313 second breast cancer as the endpoint. This secondary analysis did confirm the association
314 between the PRS₃₁₃ and second breast cancer risk (HR per SD=1.13, 95%CI=1.01-1.27), but
315 with a lower estimate than in our cohort. The lower estimate may be explained by the inclusion
316 of the ipsilateral breast cancers, which may be more likely to be recurrences than new primary
317 breast cancers compared to CBCs. Indeed, when we used ipsilateral breast cancer as the
318 outcome in our BCAC cohort, we found no association with the PRS₃₁₃ (HR=1.02, 95%CI=0.90-
319 1.15).

320

321 The association between the PRS₃₁₃ and CBC risk (OR per SD=1.30; 95%CI=1.26-1.35) in the
322 BCAC database was weaker (expressed in terms of an OR) than was found for first breast
323 cancer among independent prospective studies (OR per SD=1.61; 95%CI=1.57-1.65). Under a
324 simple polygenic model, the relative risk would be expected to be similar for the second breast
325 cancer. The attenuated estimate for CBC might however be explained by several factors. Some
326 attenuation of the estimate might have been due to dilution in the end-point definition, *i.e.*, if
327 some of the CBCs were metastases. Previous studies investigating the clonal relatedness of
328 first breast cancers and CBCs using tumor sequencing have shown that 6-12% of CBCs
329 represent metastases^{18; 19}. This hypothesis would be consistent with our finding of a slightly
330 stronger association between the PRS₃₁₃ and late CBCs, diagnosed >five years after the first
331 breast cancer, than for early CBCs, diagnosed ≤five years after the first cancer, since the latter
332 are more likely to be metastases. In addition, 3-5% of the breast cancer patients will be *BRCA1*

333 or *BRCA2* mutation carriers^{20; 21}, who have high CBC risks. It has been shown that the relative
334 risk associated with PRS is lower (for the first breast cancer) for *BRCA1* and *BRCA2* mutation
335 carriers than in the general population²², diluting the overall relative risk for CBC. More
336 generally, it is possible that the CBC association may be attenuated due to the effect of other,
337 unmeasured, genetic or other risk factors. If the risks are high, cases with higher PRS₃₁₃ will
338 have, on average, lower values of other risk factors, due to elimination of the highest risk
339 individuals, again attenuating the CBC association. Finally, given the limited information on
340 family history in our dataset, the estimate could have been biased due to a family history effect
341 not detected in our data.

342
343 There was some suggestion that the relative risk associated with PRS₃₁₃ decreased with
344 younger age, ($P_{\text{trend}}=.05$), and, specifically, was lower for women aged <40 years (HR per
345 SD=1.13; 95%CI=0.98-1.31). Interestingly, Mavaddat et al⁷ also found a lower relative risk
346 below age 40 for first breast cancer. This effect may reflect the different characteristics of breast
347 cancers at young ages, both in terms of germline susceptibility and pathology^{23; 24}. For example,
348 the proportion of ER-negative breast cancers is higher at young ages, and the PRS is less
349 predictive for ER-negative disease^{6; 7; 24}.

350
351 In the logistic regression analyses in Asian women, the association between the PRS₃₁₃ and
352 CBC risk was slightly weaker than in European women. This finding is consistent with a study
353 investigating the association between a 287-variant PRS and first breast cancer risk in the Asian
354 population²⁵, which showed an attenuated OR in Asian women (OR=1.52, 95%CI=1.49-1.56)
355 compared to European women (OR=1.61, 95%CI=1.57-1.66). The lower estimate for Asian
356 women might reflect the fact the PRS₃₁₃ was developed in European populations, and the
357 different LD structure in Asians may attenuate the association since the variants in the PRS are
358 likely to be surrogates for the causal variants. Other explanations for the attenuated estimate

359 may be the slightly younger age at first breast cancer diagnosis and the higher proportion ER-
360 negative CBCs in Asian women compared to European women in our study. Finally, the
361 imputation quality for variants was somewhat lower, on average, for the Asian than for the
362 European dataset, with three variants on OncoArray and four variants on ICOGs with an
363 imputation quality score < 0.3 (Table S3). Nevertheless, we included those variants in the PRS
364 for both European and Asian women, to keep the PRS comparable between ethnicities and
365 studies. Future studies including larger numbers of Asian women, and women of other
366 ethnicities, are needed to generate population-specific PRSs and to validate our findings in
367 these groups.

368
369 A major strength of this study is the very large sample size in the BCAC dataset, including
370 genotype information for ~150,000 women and a large number of CBC events. A limitation of
371 this study is missing data on the patient, tumor, and treatment characteristics, which reduces
372 the power of the multivariable Cox regression analyses and interaction analyses. In addition,
373 registration of CBC was not complete; the 10-year cumulative CBC incidence was 2.2% in the
374 BCAC dataset, compared to 3.8% using complete data from the Netherlands Cancer Registry¹.
375 For this reason, we estimated relative risk estimates using the BCAC data and applied these to
376 external registry data to obtain absolute risk estimates. The underreporting of CBC should not
377 bias our HR estimates, given that the event rate is low and reporting of CBC is unlikely to be
378 related to the PRS₃₁₃. Moreover, we reran the cohort analysis in the subset of countries with a
379 10-year cumulative CBC incidence ≥ 3.0% in the BCAC dataset, and the estimates were very
380 similar to the main analyses (HR per SD = 1.23, 95% CI = 1.14-1.33) (Figure S3).

381
382 In conclusion, the PRS₃₁₃ is predictive for the development of CBC. We found no evidence for
383 confounding or effect modification by other previously established CBC risk factors. The PRS₃₁₃
384 is therefore likely to be an independent risk factor for CBC. Since the predictive ability of the

385 PRS on its own is modest, it should be combined with other breast cancer risk factors to provide
386 more useful CBC risk prediction models. More accurate risk prediction will help identify women
387 at high CBC risk who will benefit from additional surveillance and/or risk reducing mastectomy,
388 and equally important, to identify those women at low risk in order to avoid unnecessary
389 surgeries.

Supplemental Data

Supplemental data include four figures, eight tables, supplement UK biobank and acknowledgements.

Data and Code Availability

Data used in this manuscript may be requested through the original providers. Data of the Breast Cancer Association Consortium may be requested for non-profit research through an application procedure with the Breast Cancer Association Consortium; more information: <http://bcac.ccge.medschl.cam.ac.uk/bcacdata/>. Data of the UK biobank needs to be requested through UK biobank; more information: <https://www.ukbiobank.ac.uk/researchers/>

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Figure 1. Estimates for contralateral breast cancer risk by percentile categories of the 313-variant PRS (PRS₃₁₃)

The figure shows the hazard ratios per SD and 95% confidence intervals for percentiles of the PRS₃₁₃ relative to the middle quintile (underlying table can be found in Table S5). The solid line denotes the estimates for contralateral breast cancer risk with the PRS₃₁₃ fitted as a continuous covariate. Coefficients to construct the PRS₃₁₃ are shown in Table S3. The PRS₃₁₃ was standardized by SD=0.61, in line with Mavaddat et al.⁷. The analyses were performed with attained age as time scale. PRS = polygenic risk score, SD = standard deviation

Figure 2. Predicted contralateral breast cancer risk by percentile of the 313-variant PRS (PRS₃₁₃) with death as competing risk

Coefficients to construct the PRS₃₁₃ are shown in Table S3. The PRS₃₁₃ was standardized by SD=0.61, in line with Mavaddat et al.⁷ The CBC incidences were calculated based on incidence data from the Netherlands Cancer Registry¹ and relative risks estimated as described in the Material and Methods. PRS = polygenic risk score, CBC = contralateral breast cancer

Figure 3. Distribution of the 313-variant PRS (PRS₃₁₃) in 62,830 control women without any diagnosis of breast cancer, 81,000 women with unilateral breast cancer, and 3,607 women with contralateral breast cancer

Coefficients to construct the PRS₃₁₃ are shown in Table S3. The PRS₃₁₃ was standardized by SD=0.61, in line with Mavaddat et al.⁷. PRS = polygenic risk score, BC = breast cancer, CBC = contralateral breast cancer, SD = standard deviation

Table 1. Association between PRSs and contralateral breast cancer risk in the cohort (N=56,068)

Polygenic risk score (PRS)	No. of CBC	HR per unit SD ^a	95%CI	P-value
PRS₇₇^b				
All CBC	1,027	1.21	1.14-1.29	<.001
Invasive CBC	923	1.21	1.13-1.29	<.001
PRS₃₁₃^b				
All CBC	1,027	1.25	1.18-1.33	<.001
Invasive CBC	923	1.24	1.16-1.32	<.001
ER-positive invasive CBC ^d	275	1.38	1.23-1.55	<.001
ER-negative invasive CBC ^d	97	0.92	0.75-1.12	.39
ER-positive PRS₃₁₃^{b,c}				
All CBC	1,027	1.23	1.16-1.31	<.001
Invasive CBC	923	1.22	1.15-1.30	<.001
ER-positive invasive CBC ^d	275	1.37	1.22-1.54	<.001
ER-negative PRS₃₁₃^{b,c}				
All CBC	1,027	1.25	1.17-1.33	<.001
Invasive CBC	923	1.24	1.16-1.33	<.001
ER-negative invasive CBC ^d	97	1.06	0.86-1.30	.58

Abbreviations: PRS = polygenic risk score, No. = number, CBC = contralateral breast cancer, HR = hazard ratio, CI = confidence interval, ER = estrogen receptor, SD = standard deviation

^a All analyses were performed with attained age as time scale

^b Coefficients to construct the PRSs are shown in Table S3. All PRSs were standardized by the same SD as was used by Mavaddat et al.⁷. The SD was 0.45 for overall breast cancer PRS₇₇, 0.61 for overall breast cancer PRS₃₁₃, 0.65 for ER-positive PRS₃₁₃, and 0.59 for ER-negative PRS₃₁₃

^c ER-specific PRSs were constructed using a hybrid method, as described by Mavaddat et al.⁷

^d Patients with ER-unknown CBC (N=551) were censored in these analyses

Table 2. Association between the 313-variant PRS (PRS₃₁₃) and contralateral breast cancer risk for subgroups

Subgroups	No. of patients	No. of CBC	HR per unit SD ^{a,b}	95%CI	P-value	P _{heterogeneity} ^{c,d}	P _{trend} ^{c,e}
All patients	56,068	1,027	1.25	1.18-1.33	<.001	-	-
Age at first breast cancer diagnosis (years)						.26	.05
<40	5,877	171	1.13	0.98-1.31	.09		
40-49	11,928	265	1.25	1.11-1.41	<.001		
50-59	16,882	320	1.22	1.09-1.36	<.001		
60+	21,381	271	1.36	1.21-1.52	<.001		
Family history (first degree relative)						.63	-
no	33,623	618	1.26	1.16-1.36	<.001		
yes	10,369	302	1.22	1.09-1.36	<.001		
Morphology						.14	-
ductal	37,324	621	1.21	1.12-1.31	<.001		
lobular	5,878	118	1.32	1.10-1.59	.002		
mixed (ductal and lobular)	2,174	46	1.52	1.15-2.02	.004		
other	3,344	70	1.20	0.96-1.50	.11		
ER-status						.13	-
negative	9,527	194	1.13	0.98-1.30	.08		
positive	38,090	670	1.28	1.19-1.38	<.001		
PR-status						.26	-
negative	13,098	244	1.16	1.03-1.32	.02		
positive	27,044	554	1.27	1.17-1.38	<.001		
HER2-status						.42	-
negative	23,787	352	1.29	1.17-1.44	<.001		
positive	4,969	60	1.45	1.13-1.85	.004		
(Neo)adjuvant chemotherapy						.60	-
no	18,110	361	1.28	1.16-1.42	<.001		
yes	18,559	363	1.24	1.12-1.37	<.001		
(Neo)adjuvant endocrine therapy						.79	-
no	10,781	242	1.28	1.13-1.44	<.001		
yes	27,322	460	1.30	1.19-1.43	<.001		
Radiotherapy						.40	-
no	11,023	188	1.33	1.15-1.53	<.001		
yes	29,142	617	1.24	1.15-1.34	<.001		

Abbreviations: PRS = polygenic risk score, No. = number, CBC = contralateral breast cancer, HR = hazard ratio, CI = confidence interval, ER = estrogen receptor, PR = progesterone receptor, HER2 = human epidermal growth factor receptor 2

^a HR for CBC risk by unit SD of PRS₃₁₃. All analyses were performed with attained age as time scale

^b Coefficients to construct the PRS₃₁₃ are shown in Table S3. The PRS₃₁₃ was standardized by standard deviation=0.61, in line with Mavaddat et al.⁷

^c The interaction between the PRS₃₁₃ and each subgroup was tested in different models including the standardized PRS₃₁₃, modifier, and interaction. Patients with unknown values were excluded from these analyses. Since attained age was used as time scale in all models, the model with age at first breast cancer only included the PRS₃₁₃ and interaction

^d P for interaction based on test for heterogeneity across categories

^e P for interaction based on a trend test with age as continuous variable

Table 3. Discriminatory ability (C-index) of the 313-variant PRS (PRS₃₁₃) and other risk factors for contralateral breast cancer risk in the cohort

	C-index (95%CI) ^{a,b}
<i>Model 1</i> PRS ₃₁₃ ^c alone	0.563 (0.547-0.586)
<i>Model 2</i> Other risk factors ^d	0.605 (0.591-0.629)
<i>Model 3</i> PRS ₃₁₃ ^c + other risk factors ^d	0.623 (0.608-0.645)

Abbreviations: PRS = polygenic risk score, CI = confidence interval

^a The Harrell's C-index was obtained by the STATA stcox postestimation command 'estat concordance', using time since first breast cancer on the time scale without taking delayed entry (prevalent cases) into account. We did not consider delayed-entry since no standard performance measures are currently available in the statistical literature to account for left-truncated follow-up time. The median of delayed entry was 0.4 years (standard deviation=2.7) in our study

^b The 95% CIs were obtained by use of the 'somersd' package in STATA

^c Coefficients to construct the PRS₃₁₃ are shown in Table S3. The PRS₃₁₃ was standardized by SD=0.61, in line with Mavaddat et al.⁷

^d Including age at first diagnosis, year of first diagnosis, family history for breast cancer in a first degree relative, and clinical characteristics of the first breast cancer (nodal status, tumor size, differentiation grade, morphology, estrogen receptor status, human epidermal growth factor receptor 2 status, chemotherapy, endocrine therapy, radiotherapy)

Table 4. Five- and ten-year cumulative risks of contralateral breast cancer by the 313-variant PRS (PRS₃₁₃) for different age groups with death as competing risk

Age at first breast cancer diagnosis (years)	5-year cumulative CBC risks (%) range by age					10-year cumulative CBC risks (%) range by age				
	5 th percentile PRS ₃₁₃	10 th percentile PRS ₃₁₃	50 th percentile PRS ₃₁₃	90 th percentile PRS ₃₁₃	95 th percentile PRS ₃₁₃	5 th percentile PRS ₃₁₃	10 th percentile PRS ₃₁₃	50 th percentile PRS ₃₁₃	90 th percentile PRS ₃₁₃	95 th percentile PRS ₃₁₃
30-34	1.9-3.1	2.1-3.4	2.7-4.5	3.6-5.9	4.0-6.5	3.1-4.1	3.4-4.5	4.5-5.9	5.9-7.7	6.5-8.5
35-39	0.8-2.1	0.9-2.3	1.2-3.0	1.5-3.9	1.7-4.3	2.1-3.5	2.3-3.8	3.0-5.0	3.9-6.6	4.3-7.2
40-44	1.5-2.8	1.7-3.1	2.2-4.1	2.9-5.3	3.2-5.9	2.8-4.6	3.1-5.0	4.1-6.6	5.3-8.6	5.9-9.4
45-49	1.4-2.5	1.5-2.7	2.0-3.6	2.6-4.7	2.9-5.2	2.5-3.9	2.7-4.3	3.6-5.6	4.7-7.4	5.2-8.1
50-54	1.4-2.8	1.5-3.0	1.9-4.0	2.6-5.2	2.8-5.8	2.8-4.5	3.0-4.9	4.0-6.4	5.2-8.4	5.8-9.3
55-59	1.6-3.1	1.8-3.4	2.3-4.5	3.1-5.9	3.4-6.5	3.1-4.8	3.4-5.2	4.5-6.9	5.9-9.0	6.5-9.9
60-64	1.7-3.3	1.9-3.6	2.5-4.7	3.3-6.2	3.6-6.8	3.3-5.0	3.6-5.4	4.7-7.1	6.2-9.3	6.8-10.2
65-70	1.5-3.2	1.6-3.5	2.1-4.6	2.8-6.1	3.1-6.7	3.2-4.1	3.5-4.5	4.6-5.9	6.1-7.7	6.7-8.5

Abbreviations: PRS = polygenic risk score, CBC = contralateral breast cancer

Coefficients to construct the PRS₃₁₃ are shown in Table S3. The PRS₃₁₃ was standardized by SD=0.61, in line with Mavaddat et al⁷. The CBC incidences for each age group were calculated based on incidence data from the Netherlands Cancer Registry¹ and relative risks estimated as described in the Material and Methods. Death was taken into account as competing risk.