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RESEARCH ARTICLE

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Association of the *CHEK2* c.1100delC variant, radiotherapy, and systemic treatment with contralateral breast cancer risk and breast cancer-specific survival

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Abstract

Background: Breast cancer (BC) patients with a germline CHEK2 c.1100delC variant have an increased risk of contralateral BC (CBC) and worse BC-specific survival (BCSS) compared to non-carriers.

Aim: To assessed the associations of CHEK2 c.1100delC, radiotherapy, and systemic treatment with CBC risk and BCSS.

Methods: Analyses were based on 82,701 women diagnosed with a first primary invasive BC including 963 CHEK2 c.1100delC carriers; median follow-up was 9.1 years. Differential associations with treatment by CHEK2 c.1100delC status were tested by including interaction terms in a multivariable Cox regression model. A multi-state model was used for further insight into the relation between CHEK2 c.1100delC status, treatment, CBC risk and death.

Results: There was no evidence for differential associations of therapy with CBC risk by CHEK2 c.1100delC status. The strongest association with reduced CBC risk was observed for the combination of chemotherapy and endocrine therapy [HR (95% CI): 0.66 (0.55–0.78)]. No association was observed with radiotherapy. Results from the multi-state model showed shorter BCSS for CHEK2 c.1100delC carriers versus non-carriers also after accounting for CBC occurrence [HR (95% CI): 1.30 (1.09–1.56)].

Conclusion: Systemic therapy was associated with reduced CBC risk irrespective of CHEK2 c.1100delC status. Moreover, CHEK2 c.1100delC carriers had shorter BCSS, which appears not to be fully explained by their CBC risk.

KEYWORDS
CHEK2 c.1100delC germline genetic variant, contralateral breast cancer risk, radiotherapy, survival, systemic treatment

1 | INTRODUCTION

Breast cancer (BC) has the highest incidence in women worldwide.[1] One of the germline variants that confer a moderate increased BC risk is the *CHEK2* c.1100delC variant,[2–4] which is found in approximately 0.7% of the Northern and Western European populations.[5] Overall, carriers of this variant are diagnosed at a younger age than non-carriers[4] and the majority develops BCs that are estrogen receptor (ER)- and progesterone receptor

(PR)-positive and human epidermal growth factor receptor 2 (HER2)-negative.[3,6] Although this BC subtype has the most favorable prognosis in the general BC population,[7] *CHEK2* c.1100delC carriers have a higher risk of developing contralateral breast cancer (CBC) and worse survival[3,4,6,8,9] compared to non-carriers.

Reasons behind these differences are still unclear. A possible explanation is that *CHEK2* c.1100delC carriers have a different response to treatment compared to non-carriers. Radiotherapy has been shown to increase the risk of CBC in the general BC population, especially in younger patients.[10] Treatment with radiotherapy causes DNA strand breaks, which are less likely to be repaired in *CHEK2* c.1100delC carriers.[11] While this might be beneficial for the treatment of the first primary cancer, carriers might be more prone to developing a CBC.[12] One case-only study showed a non-significant increased risk for developing CBC after treatment with radiotherapy in *CHEK2* c.1100delC carriers versus non-carriers, but due to the small study size, the associations in the younger population could not be investigated.[13] Only one other small study reported on the association between radiotherapy and CBC risk by *CHEK2* c.1100delC status.[8]

On the other hand, less is known about whether the impact of systemic therapy on CBC risk and survival differs by CHEK2 c.1100delC status. A population-based study showed a significant decrease in CBC risk following chemotherapy and endocrine therapy in BC overall.[14] One single-hospital study also found a decreased risk of CBC after chemotherapy use in *CHEK2* c.1100delC carriers, and did not find evidence for a differential association by *CHEK2* c.1100delC status.[15] That study also found no evidence for a differential impact of chemotherapy on survival.[15]

Given this uncertainty, our aim was to assess, within a large international cohort, potential differential associations of treatment given for the first primary BC (i.e., radiotherapy, chemotherapy, and endocrine therapy) by *CHEK2* c.1100delC status with CBC risk and to investigate whether the worse breast cancer-specific survival (BCSS) so far reported in carriers is explained solely by the increased CBC risk.

2 | MATERIALS AND METHODS

2.1 | Study population

We used data from the Breast Cancer Association Consortium (BCAC), selected women of European ancestry, diagnosed with a first primary invasive BC between 1980 and 2018; exclusion criteria are shown in Figure 1. The main analyses were based on 82,701 BC patients from 58 BCAC studies (Table S1). All individual studies were approved by the appropriate institutional review boards and/or medical ethical committees. Written informed consent was obtained from all study participants.

Previous analyses investigating the relationship between *CHEK2* c.1100delC status, risk of CBC, and mortality have been based on a subset of patients genotyped with Taqman.[3,4] In particular, the current study includes most carriers from the Weischer et al. study ($n = 459$)[4] and from the Kriege et al. study ($n = 193$),[15] but is based on a larger number of BC patients and includes updated follow-up data.

2.2 | Data collection

All relevant clinical-pathological and treatment information, as well as outcome information, was collected by individual studies and harmonized by the BCAC Survival, Pathology and Treatment Working Group at the Netherlands Cancer Institute, Amsterdam, the Netherlands, in collaboration with the individual studies before incorporation into the BCAC database (version 13, May 2021). *CHEK2* c.1100delC status was obtained from five different sources: BRIDGES sequencing data,[16] Taqman and iPLEX genotyping[3,4,17] (56.5% of the included study individuals: 0.9% *CHEK2* c.1100delC carriers and 55.6% non-carriers, respectively), and imputed genotypes from OncoArray[18] (32.0% of the included study individuals: 0.02% defined as CHEK2 c.1100delC carriers and 31.8% defined as non-carriers based on imputed dosages) or iCOGS[19] (the remaining 11.5% of the included study individuals: 0.1% defined as *CHEK2* c.1100delC carriers and 11.4% as non-carriers based on imputed dosages) as described in the Supplementary Methods.

2.3 | Statistical analyses

Multiple imputation, performed using R package MICE (version 3.13.0), was used to handle missing values in clinical and pathological variables. Details are given in the Supplementary Methods and Table S2. Descriptive statistics are shown as mean ± standard deviation (SD) or median and interquartile range (IQR). We used Pearson's chi-squared test for categorical data and Kruskal–Wallis test for continuous data to calculate differences in patients' characteristics. The primary study outcomes were time to CBC and BCSS (time to death due to BC).

Hazard ratios (HRs) and 95% confidence intervals (CIs) for the association of treatment given for the first primary BC (radiotherapy and/or type of systemic treatment) and *CHEK2* c.1100delC status with time to CBC

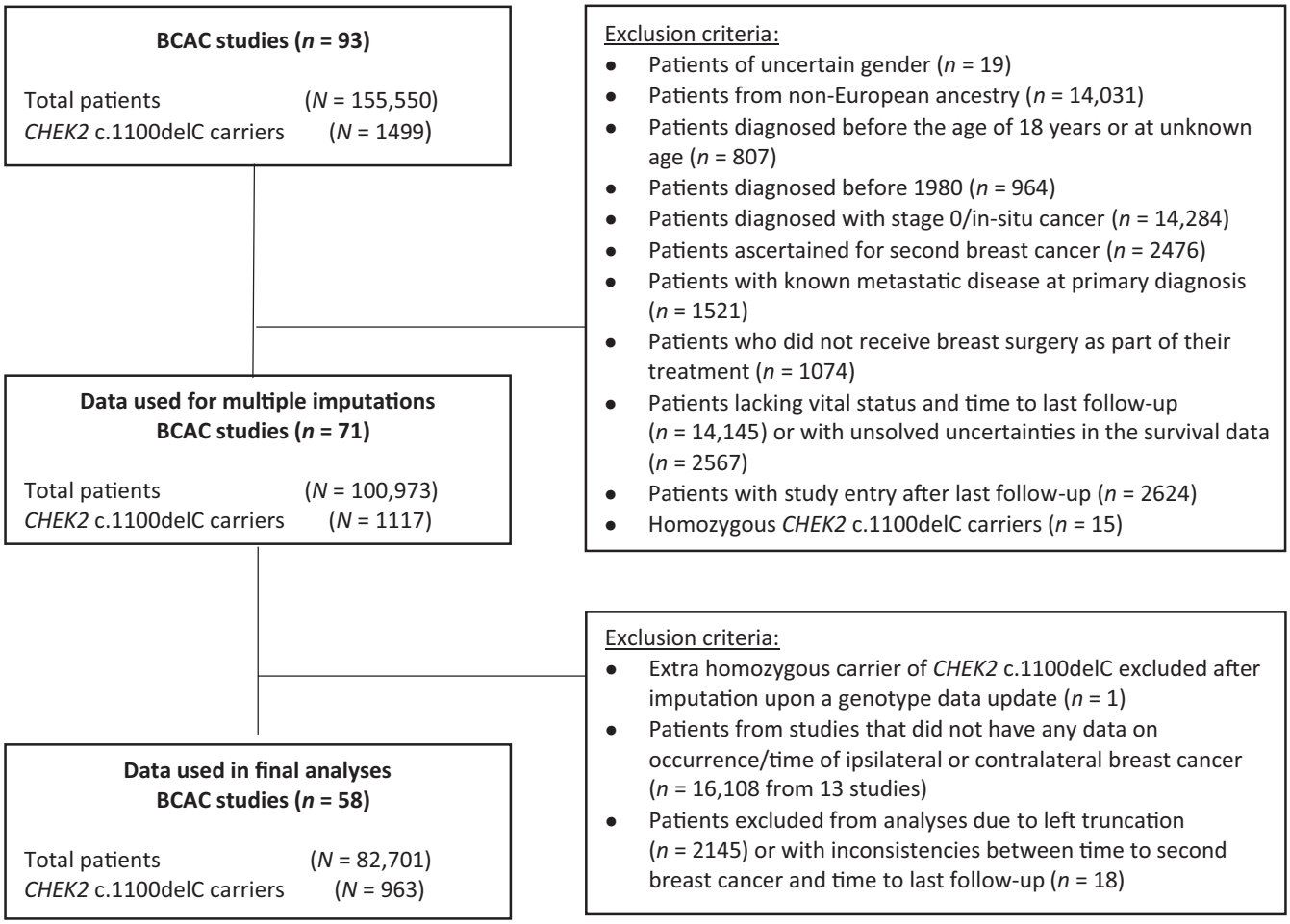

FIGURE 1 Data flowchart of inclusion and exclusion of patients with breast cancer from the Breast Cancer Association Consortium (BCAC) database.

were estimated via Cox regression models allowing for delayed entry, stratified by country and adjusted for age at first primary BC diagnosis, tumor size, nodal status, grade, and ER status. Since ER status is known to violate the proportionality hazards assumption and because the majority of *CHEK2* c.1100delC carriers develop ER-positive BC, we performed an additional main analysis restricted to patients diagnosed with a first primary ER-positive BC. We assumed that patients with unknown CBC status did not develop a CBC during follow-up and that for CBC cases with unknown time from first primary BC to CBC diagnosis, CBC occurrence was at last available follow-up.

Time at risk started either 3 months after first primary BC diagnosis or at study entry if entry was more than 3 months after first primary BC diagnosis, and ended at time of CBC, death or last follow-up, whichever came first. We tested for potential differential association of adjuvant and/or neo-adjuvant therapy on CBC risk according to *CHEK2* c.1100delC status by including an interaction term between treatment (radiotherapy or systemic treatment) variable and *CHEK2* c.1100delC status in the model. CBC risk analyses were stratified by two follow-up time intervals: (i) the first 5 years after BC diagnosis and (ii) starting 5 years after BC diagnosis.

To gain further insight into the relation between *CHEK2* c.1100delC status, treatment given for the first primary BC, CBC risk, and death, we used a multi-state model in the framework of the Cox model, with diagnosis of the first primary BC as initial state, diagnosis of CBC as intermediate (transient) state, and death due to BC, death due to other causes, and death due to unknown causes as absorbing states (Figure 2), as specified in the Supplementary Methods.

The main CBC risk and multi-state analyses were performed on imputed datasets. Complete-case analyses (excluding study subjects with missing values in any of the variables included in the models) were performed as sensitivity analyses. Additional analyses were restricted to: (a) patients diagnosed with first primary BC from 2000 onwards to reduce heterogeneity in treatment regimens; (b) patients diagnosed at age 40 or younger to see if the association with radiotherapy was stronger in

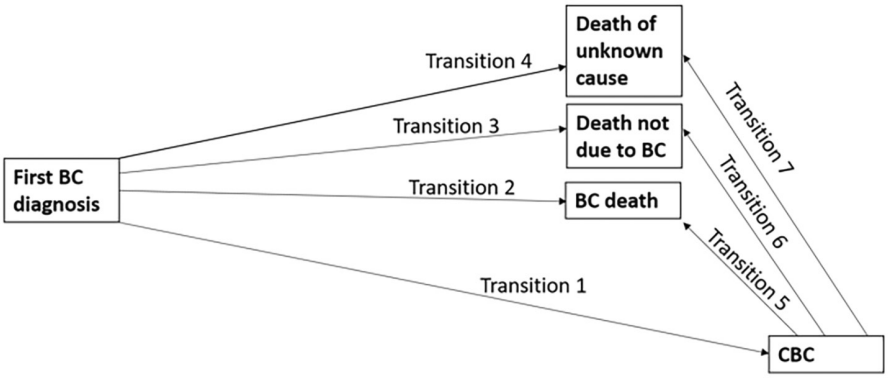

FIGURE 2 Graphical representation of the multi-state model. BC, breast cancer; CBC, contralateral breast cancer.

this subgroup, as reported previously in the general BC population.[10]

3 | RESULTS

This study included data from 963 *CHEK2* c.1100delC carriers and 81,738 non-carriers. Patients carrying the *CHEK2* c.1100delC variant were diagnosed with a first primary invasive BC at a younger age (median age 52 years in carriers compared to 56 years in non-carriers) and in earlier calendar years (36.4% of carriers was diagnosed before 2000, compared to 27.6% of the non-carriers). The tumors of carriers were larger at time of diagnosis and were more often lymph node-positive, grade 2, and ER- and PR-positive than in non-carriers. Furthermore, carriers more often underwent a mastectomy as part of their treatment compared to non-carriers and more often did not receive any systemic therapy compared to the non-carriers (Table 1).

3.1 | Contralateral breast cancer

CHEK2 c.1100delC carriers were diagnosed with CBC at younger age and in earlier calendar years. Overall, the characteristics of the CBC were similar between the non-carriers and carriers (Table S3). However, *CHEK2* c.1100delC carriers more often had positive nodes at CBC diagnosis than non-carriers ($p = 0.02$).

3.2 | Contralateral breast cancer risk by treatment and *CHEK2* c.1100delC carrier status

There was no evidence for a differential association of *CHEK2* c.1100delC status by radiotherapy (Tables 2 and 3: p-value for interaction = 0.31 in all patients and p-value for interaction = 0.99 in ER-positive patients) or systemic therapy (p-value for interaction = 0.46 in all patients and p-value for interaction = 0.68 in ER-positive patients). Moreover, we did not find an association of radiotherapy with CBC risk [HR (95% CI): 1.07 (0.94–1.21), $p = 0.33$ in all BC patients and 1.07 (0.92–1.25), $p = 0.35$ in ER-positive BC patients]. Regarding systemic therapy, we observed that chemotherapy alone [HR (95% CI): 0.77 (0.62–0.96), $p = 0.02$ in all BC patients and 0.73 (0.52–1.03), $p = 0.07$ in ER-positive BC patients], endocrine therapy alone [HR (95% CI): 0.70 (0.58–0.83), $p < 0.001$ in all BC patients and 0.66 (0.54–0.81), $p < 0.001$ in ER-positive BC patients], and the combination of both [HR (95% CI): 0.65 (0.55–0.78), $p < 0.001$ in all BC patients and 0.65 (0.52–0.82), $p < 0.001$ in ER-positive BC patients] were associated with lower CBC risk compared to women who did not receive any systemic therapy as part of their treatment.

Results of analyses for patients diagnosed at the age of 40 years or younger or for patients diagnosed from 2000 onwards were in line with the results of the main analyses (Tables S4 and S5). Complete-case analyses results were consistent with the corresponding results of the imputed data analyses (Tables S6–S9), except for the association with radiotherapy in patients diagnosed at the age of 40 years or younger. For these patients, radiotherapy was significantly associated with increased CBC risk in the complete-case analysis with follow-up starting 5 years after diagnosis of the first primary BC [Table S7; HR (95% CI): 2.12 (1.06–4.22), $p = 0.03$]. In addition, interaction terms between treatments and *CHEK2* c.1100delC status could not be properly estimated in some of the complete-case analyses, due to insufficient data. These included, among others, the analysis based on all patients with follow-up starting at 5 years after BC diagnosis; the analysis restricted to patients diagnosed at the age of 40 years or younger and based on the total follow-up; and the analysis restricted to ER-positive BC with follow-up starting 5 years after BC diagnosis (Tables S10–S12).

TABLE 1 Clinical, tumor and treatment characteristics for the first primary BC by *CHEK2* c.1100delC carrier status.

Characteristics	Non-carriers	*CHEK2* c.1100delC carriers	*p*-value
Number of patients, *n*	81,738	963	
Number of patients diagnosed with CBC, *n* (%)	1757 (2.1)	59 (6.1)	
Number of patients diagnosed with ipsilateral BC, *n* (%)[a]	517 (0.6)	6 (0.6)	
Total FU time, years (IQR)	9.2 (5.3–13.6)	9.6 (5.5–13.9)	
Clinical risk factors			
Age at diagnosis, *y*, median (IQR)	56 (47–64)	52 (44–61)	<0.001
Age at diagnosis, *n* (%)			<0.001
<40 years	9471 (11.6)	171 (17.8)	
40–50 years	19,978 (24.4)	277 (28.8)	
50–60 years	23,044 (28.2)	266 (27.6)	
>60 years	29,245 (35.8)	249 (25.9)	
Year of diagnosis, *n* (%)			<0.001
1980–1989	2259 (2.8)	48 (5.1)	
1990–1999	20,055 (24.8)	297 (31.3)	
2000–2009	45,910 (56.7)	492 (51.8)	
≥2010	12,781 (15.8)	113 (11.9)	
Missing, *n*	733	13	
Tumor characteristics			
Tumor size, *n* (%)			0.01
≤2 cm	40,263 (63.0)	421 (58.6)	
>2 and ≤5 cm	20,977 (32.8)	273 (38.0)	
>5 cm	2718 (4.3)	24 (3.3)	
Missing, *n*	17,780	245	
Lymph node status, *n* (%)			<0.001
Negative	42,079 (61.4)	439 (54.8)	
Positive	26,456 (38.6)	362 (45.2)	
Missing, *n*	13,203	162	
Grade, *n* (%)			0.01
Grade 1	12,572 (19.1)	112 (15.3)	
Grade 2	31,594 (48.1)	388 (53.0)	
Grade 3	21,536 (32.8)	232 (31.7)	
Missing, *n*	16,036	231	
Morphology, *n* (%)			0.16
Ductal	52,127 (74.0)	659 (77.5)	
Lobular	10,596 (15.0)	116 (13.7)	
Medullary	619 (0.9)	3 (0.4)	
Mixed (ductal and lobular)	3032 (4.3)	37 (4.4)	
Mucinous	895 (1.3)	7 (0.8)	
Papillary	160 (0.2)	22 (0.1)	
Tubular	908 (1.3)	1 (0.6)	
Other	2111 (3.0)	5 (2.6)	
Missing, *n*	11,290	113	
ER status, *n* (%)			<0.001
Negative	13,918 (20.4)	93 (11.8)	
Positive	54,481 (79.7)	694 (88.2)	
Missing, *n*	13,339	176	

TABLE 1 (Continued)

Characteristics	Non-carriers	*CHEK2* c.1100delC carriers	*p*-value
PR status, *n* (%)			<0.001
Negative	19,128 (32.1)	169 (24.5)	
Positive	40,548 (68.0)	520 (75.5)	
Missing, *n*	22,062	274	
HER2 status, *n* (%)			0.55
Negative	37,395 (83.5)	418 (82.5)	
Positive	7376 (16.5)	89 (17.6)	
Missing, *n*	36,967	456	
Treatment			
Surgery, *n* (%)			<0.001
Breast conserving surgery	23,706 (43.3)	244 (36.3)	
Mastectomy	16,129 (29.4)	259 (38.5)	
Type unknown	15,330 (27.6)	169 (25.2)	
Missing, *n*	26,573	291	
Radiotherapy, *n* (%)			0.36
No	13,163 (26.0)	181 (27.6)	
Yes	37,479 (74.0)	474 (72.4)	
Missing, *n*	31,096	308	
Systemic therapy, *n* (%)			<0.001
No systemic therapy	4996 (11.2)	94 (17.0)	
CT, no ET	7501 (16.8)	88 (15.9)	
ET, no CT	16,976 (38.1)	153 (27.7)	
Both CT and ET	15,116 (33.9)	218 (39.4)	
Missing, *n*	37,149	410	
Trastuzumab, *n* (%)			0.96
No	37,466 (95.4)	478 (95.2)	
Yes	1819 (4.6)	24 (4.8)	
Missing, *n*	42,453	461	

Note: Percentages are only on observed, non-missing data, and may not total 100 because of rounding.

Abbreviations: CBC, contralateral breast cancer; CT, chemotherapy; ER, estrogen receptor; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; PR, progesterone receptor.

[a]Data component not actively collected in BCAC.

3.3 | *CHEK2* c.1100delC carrier status, contralateral breast cancer, and survival trajectories

CHEK2 c.1100delC carriers versus non-carriers had an almost 2.4 fold risk of developing a CBC [HR (95% CI): 2.37 (1.82–3.08), $p < 0.001$ in all patients and 2.55 (1.87–3.48), $p < 0.001$ in patients with an ER-positive first primary BC; Table 4] and a 1.3-fold risk of BC death after censoring for CBC occurrence [HR (95% CI): 1.30 (1.09–1.56), $p = 0.003$ in all patients and 1.38 (1.12–1.71), $p = 0.003$ in patients with an ER-positive first primary BC; Table 4]. There was no evidence for association of *CHEK2* c.1100delC carrier status with other transitions. Results from the analyses restricted to patients diagnosed with first primary BC from 2000 onwards were in line with the results from the main analyses (Table S15).

Regarding treatment, radiotherapy was associated with lower risk of death due to causes other than BC or unknown causes, while there was no significant association with BC-specific death (Tables S13–S15). Endocrine therapy alone was associated with a significantly decreased risk of BC-specific death (particularly in patients diagnosed with an ER-positive first primary BC) and with a highly significantly decreased risk of death due to unknown causes. The combination of endocrine therapy and chemotherapy was associated with decreased risk of BC death (in patients diagnosed with an ER-positive first

TABLE 2 Contralateral breast cancer risk (hazard ratio) by treatment for first primary breast cancer and *CHEK2* c.1100delC status. Stratified by time since first primary breast cancer diagnosis.

	Total follow-up time			<5-year follow-up			>5 years follow-up		
No of patients	82,701			73,354			62,688		
No of CBC events	1816			656			1160		
	HR (95% CI)	*p*-value	*p*-int	HR (95% CI)	*p*-value	*p*-int	HR (95% CI)	*p*-value	*p*-int
CHEK2 c.1100delC status	2.37 (1.82–3.08)	<0.001		3.08 (2.12–4.48)	<0.001		1.93 (1.33–2.80)	<0.001	
Radiotherapy			0.31			0.30			0.77
No radiotherapy	Ref			Ref			Ref		
Radiotherapy	1.07 (0.94–1.21)	0.33		0.98 (0.81–1.19)	0.84		1.12 (0.96–1.31)	0.16	
Systemic therapy			0.46			0.70			0.39
No systemic therapy	Ref			Ref			Ref		
CT, no ET	0.77 (0.62–0.96)	0.02		0.58 (0.41–0.83)	0.003		0.90 (0.70–1.15)	0.39	
ET, no CT	0.70 (0.58–0.83)	<0.001		0.62 (0.46–0.84)	0.002		0.73 (0.59–0.91)	0.005	
Both CT and ET	0.65 (0.55–0.78)	<0.001		0.50 (0.37–0.68)	<0.001		0.75 (0.62–0.93)	0.007	

Note: Adjusted for age at diagnosis, ER status, tumor size, nodal status and grade of first primary breast cancer.

Abbreviations: CBC, contralateral breast cancer; CT, chemotherapy; ER, estrogen receptor; ET, endocrine therapy; *p*-int, *p*-value for the comparison of a model including an interaction term between *CHEK2* c.1100delC status and a specific treatment (radiation or systemic treatment) with a model without any interaction term.

TABLE 3 Contralateral breast cancer risk (hazard ratio) by treatment for first primary BC and *CHEK2* c.1100delC status in ER-positive BC patients. Stratified by time since first primary breast cancer diagnosis.

	Total follow-up time			<5-year follow-up			>5 years follow-up		
No. of patients	55,175			51,146			41,269		
No. of CBC events	1133			427			706		
	HR (95% CI)	*p*-value	*p*-int	HR (95% CI)	*p*-value	*p*-int	HR (95% CI)	*p*-value	*p*-int
CHEK2 c.1100delC status	2.55 (1.87–3.48)	<0.001		3.42 (2.24–5.22)	<0.001		1.94 (1.22–3.08)	0.005	
Radiotherapy			0.99			0.47			0.41
No radiotherapy	Ref			Ref			Ref		
Radiotherapy	1.07 (0.92–1.25)	0.35		1.04 (0.81–1.34)	0.75		1.09 (0.90–1.32)	0.36	
Systemic therapy			0.68			0.91			0.96
No systemic therapy	Ref			Ref			Ref		
CT, no ET	0.73 (0.52–1.03)	0.07		0.62 (0.38–1.03)	0.06		0.80 (0.52–1.23)	0.31	
ET, no CT	0.66 (0.54–0.81)	<0.001		0.55 (0.40–0.77)	<0.001		0.73 (0.57–0.94)	0.02	
Both CT and ET	0.65 (0.52–0.82)	<0.001		0.48 (0.34–0.69)	<0.001		0.77 (0.58–1.03)	0.08	

Note: Adjusted for age at diagnosis, nodal status, size category and grade of first primary breast cancer.

Abbreviations: CT, chemotherapy; ER, estrogen receptor; ET, endocrine therapy; *p*-int, *p*-value for the comparison of a model including an interaction term between *CHEK2* c.1100delC status and a specific treatment (radiotherapy or systemic treatment) with a model without any interaction term.

primary BC), with risk of death due to causes other than BC and had the strongest protective association against death due to unknown causes (Table S14). The corresponding complete-case analyses showed similar patterns of association (Tables S16–S18).

4 | DISCUSSION

The main goal of this study was to assess potential differential associations of treatment by *CHEK2* c.1100delC status with CBC risk and to investigate if the poorer survival in *CHEK2* c.1100delC carriers may be explained alone by the occurrence of CBC. The Breast Cancer Association Consortium provided a unique resource of 963 carriers of this single *CHEK2* variant to study this question in more detail.

These data did not support the hypothesis of differential associations of treatment with CBC risk by *CHEK2* c.1100delC status. As expected, systemic therapy was found to decrease CBC risk, with the strongest association in the first 5 years after first primary BC diagnosis, when

TABLE 4 Multi-state model in all breast cancer patients and in patients diagnosed with a first primary ER-positive breast cancer: hazard ratio for the comparison of *CHEK2* c.1100delC carriers versus non-carriers for each transition.

Analysis	Transition	Description	HR (95% CI)	*p*	Cases	Events
All BC patients	1	First primary BC → CBC	2.37 (1.82–3.08)	<0.001	82,701	1816
	2	First primary BC → BC death	1.30 (1.09–1.56)	0.003		7467
	3	First primary BC → death not due to BC	1.00 (0.75–1.34)	0.98		4247
	4	First primary BC → death of unknown cause	1.07 (0.76–1.49)	0.70		3548
	5	CBC → BC death	1.23 (0.72–2.10)	0.46	1816	281
	6	CBC → death not due to BC	0.60 (0.14–2.52)	0.49		124
	7	CBC → death of unknown cause	1.21 (0.41–3.53)	0.73		94
Patients diagnosed with primary ER-positive BC	1	First primary BC → CBC	2.55 (1.87–3.48)	<0.001	55,175	1133
	2	First primary BC → BC death	1.38 (1.12–1.71)	0.003		4266
	3	First primary BC → death not due to BC	1.13 (0.81–1.56)	0.47		2817
	4	First primary BC → death of unknown cause	0.97 (0.63–1.48)	0.87		2090
	5	CBC → BC death	1.49 (0.79–2.81)	0.21	1133	167
	6	CBC → death not due to BC	0.89 (0.20–4.06)	0.89		80
	7	CBC → death of unknown cause	0.61 (0.14–2.79)	0.53		55

Note: The models included age at first primary BC diagnosis, nodal status, tumor size, grade, radiotherapy and systemic treatment given for the first primary BC as covariates. The model based on all BC patient included ER status of the first primary BC as additional covariate. Baseline hazards were allowed to vary across country and transition. All the estimates from the model are shown in Tables S13 and S14.

Abbreviations: BC, breast cancer; CBC, contralateral breast cancer; CI, confidence interval; ER, estrogen receptor; HR, hazard ratio.

endocrine therapy is likely to be ongoing.[14,20] Overall, we did find that the combination of endocrine therapy with chemotherapy resulted in the largest reduction in CBC risk, which has been previously reported.[14] The lack of evidence for a differential association of systemic therapy with CBC risk by *CHEK2* c.1100delC status suggests that carriers experience a similar beneficial effect as non-carriers. This is in line with previous studies in *CHEK2* c.1100delC carriers.[15,21,22]

In addition, we did not find a significant association of radiotherapy with CBC risk. This lack of association is in contrast with previous studies in sporadic BC patients, which showed that radiotherapy is a contributor to CBC risk, especially when treatment was administered at a younger age.[10,23–25] One explanation for this might be the change of radiation techniques over time. However, analyses restricted to patients diagnosed from the year 2000 onwards, when treatment regimens were expected to be more homogeneous, showed similar results as were found in the main analyses. Therefore, although observational—and non-randomized—studies like the present cannot rebut hypotheses of causality, these changes are unlikely to be the reason behind the lack of association between radiotherapy and CBC risk in our study.

In line with previous studies,[3,4] we found a greater than twofold increased risk of CBC in *CHEK2* c.1100delC carriers compared to non-carriers. This is consistent with the reported increase in risk of a first primary BC,[2,16] suggesting that genetic variants that predispose to the development of a first primary BC will also predispose to the development of a CBC. We also observed a shorter BCSS in *CHEK2* c.1100delC carriers compared to non-carriers, after accounting for CBC occurrence, age at diagnosis of the first primary BC and tumor characteristics. This suggests that the shorter BCSS in *CHEK2* c.1100delC carriers versus non-carriers is partly explained by a component other than the established prognostic factors. Moreover, *CHEK2* c.1100delC carriers were on average diagnosed in earlier calendar years compared to non-carriers. Therefore, carriers probably received less efficacious chemotherapy and endocrine therapy compared to non-carriers, which could have affected survival.

The main strengths of our study are the large sample size, including information about tumor pathology, treatment, time to CBC and survival, and a median follow-up of over 9 years. In addition, the use of a multi-state model provides important advantages compared to individual survival models with different endpoints. By modeling all events of interest together, the multi-state model

gives insight on how intermediate events, such as CBC, affect survival. Moreover, it allows estimation of associations with transition-specific treatment and covariates, thereby providing insight on whether and to what extent the associations change across transitions and corresponding endpoints. Most of the studies were hospital- or population-based, and most BC patients were unaware of a *CHEK2* variant, which we determined in the research setting. Therefore, it is highly unlikely that knowledge of carrier status could have affected clinical data collection.

There are some limitations to our study that need to be acknowledged. Between studies there was minor heterogeneity in the definition of stage, grade, and cut-offs for ER, PR, and HER2 status, which would have affected both carriers and non-carriers to a similar extent and is unlikely to have impacted our conclusions. Many of the variables related to tumor characteristics and treatment had large proportions of missing values. Complete-case analyses have less power to detect the associations of interest and might be biased if case data are not missing completely at random.[26] We addressed the missing data problem by employing multiple imputation,[26] which should provide unbiased estimates, assuming that data are missing at random and that imputation models are correctly specified. Analyses restricted to complete-case data yielded results that were mostly consistent with the results based on imputed data. In addition, in some complete-case analyses, the number of *CHEK2* c.1100delC carriers was too low to properly estimate the interaction terms. This underlines the importance of the analyses based on imputed data, which avoids losses in the number of cases and events in the analyses. We also did not consider type of chemotherapy or endocrine therapy in the analyses, nor had we information about ovarian function suppression. Moreover, information about the occurrence of primary ipsilateral BCs was very limited and could not be properly accounted for in our analyses. However, based on the available information, there was no difference in the proportion of ipsilateral BC between *CHEK2* c.1100delC carriers and non-carriers (0.6% in both groups) and is unlikely to have had a major impact on our BCSS results. An additional limitation was the lack of information on cause of death for about 25% of those who had died. This would result in a loss of power to detect associations with BCSS if most of the deaths of unknown causes were due to BC. However, this would, at worst, dilute our results rather than leading to false-positive significant associations with BCSS. Finally, while we accounted for several established BC prognostic factors in our analyses, we cannot exclude the presence of residual bias affecting to some extent our results. An example of such bias is known as "indication bias," which applies to the presence of an indication which causes or affects the outcome of interest.[27] This could explain some of the unexpected results for the association of radiotherapy and systemic treatment with death-related outcomes, in case treatment decisions are influenced by the presence/absence of certain conditions or morbidities in such a way that patients receiving the treatment are less likely to die from other causes than BC. While indication bias could have affected the treatment-related effects on mortality, it is less likely to be an issue for the association of *CHEK2* c.1100delC status and treatment with CBC risk and survival.

In conclusion, the results of our study did not provide evidence for differential associations with radiation or systemic therapy by *CHEK2* c.100delC status on CBC risk. This suggests that associations of these treatments with CBC risk are similar between carriers and non-carriers. Furthermore, we confirmed the presence of a risk component for BC-specific death in *CHEK2* c.1100delC carriers which is not explained by CBC occurrence or characteristics of the first primary BC. Genotyping of *CHEK2* c.1100delC in patients of ongoing clinical trials would allow the evaluation of treatment response in detail and determine any impact of the *CHEK2* c.1100delC variant on the efficacy of BC treatment. In addition, studies focusing on, for example, the molecular copy number aberration profile of *CHEK2*-related tumors should further shed light on potential biological mechanisms underlying the observed increased CBC risk and possible worse survival in CHEK2 c.1100delC carriers.

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ETHICS STATEMENT

All individual studies were approved by the appropriate institutional review boards and/or medical ethical committees. Written informed consent was obtained from all study participants.

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. To receive access to the data, a concept form must be submitted, which will then be reviewed by the BCAC Data Access Coordination Committee (DACC); see http://bcac.ccge.medschl.cam.ac.uk/bcacdata/.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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