Review Article

CHEK2 variants, breast cancer, and implications for management: a narrative review

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Background and Objective: Around 6% of female breast cancer (BC) cases are attributed to an inherited predisposition. Of the genes associated with an increased risk of BC, *CHEK2* stands out as one of those most commonly identified. This review discusses various aspects of the association between the *CHEK2* pathogenic variants (PVs) and BC.

Methods: This narrative review involved a comprehensive search of the literature in the PubMed, Embase, Google Scholar and the Latin American and the Caribbean Literature on Health Sciences (LILACS) databases. Original articles, reviews, meta-analyses, medical society consensuses and guidelines published in English were included.

Key Content and Findings: This review highlights the complexity and challenges involved in managing *CHEK2* PV carriers. When assessing the risk of BC in these individuals, family history and the type of mutation (either missense or protein-truncating) are relevant factors, emphasizing the need for personalized risk assessments. Few studies involving large cohorts and focusing on different outcomes were identified, specifically in *CHEK2* PV carriers. Consequently, further studies with *CHEK2* PV carriers are required that take genetic diversity into consideration, since the available data originate predominantly from cohorts with European ancestry.

Conclusions: This review provides up-to-date evidence on the association between *CHEK2* PVs and BC and its implications for the counseling and management of carriers.

Keywords: Breast cancer (BC); *CHEK2* gene; hereditary breast cancer; moderate-penetrance gene; risk-reducing

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Introduction

The Global Cancer Observatory (GLOBOCAN) estimates that 2.3 million new cases of female breast cancer (BC) occurred worldwide in 2022, corresponding to 11.6% of all cancer cases (1). In that same year, 357,200 new cases were reported in China (2). In 2024, 73,000 new cases are expected to occur in Brazil (3) and 310,720 in the United States (US) (4). Approximately 6% of BC cases in women are hereditary (5-7). This means that these women have inherited a pathogenic or likely pathogenic germline variant that increases their risk of developing BC. Identification of a pathogenic or likely pathogenic variant (PV) at molecular testing confers positivity (8,9) and the implications for management are the same (9). As in previous studies, these categories are jointly referred to here as PVs (5,10-15).

Currently, multigene panel testing (MGPT) is the standard laboratory method used to investigate hereditary cancer predisposition syndromes, with *CHEK2* being identified as one of the most common genes associated with BC susceptibility (5,6,16,17). The tumor suppressor

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Table 1 Strategies used in the literature search

Items	Specification
Date of search	01 February 2024 to 31 August 2024
Databases and other sources searched	PubMed, Embase, Google Scholar, LILACS
Search terms used	*CHEK2* gene, breast cancer, breast density, risk factors, male breast cancer, contralateral breast cancer, survival, polygenic risk score, mammographic density, moderate penetrance genes, surveillance, risk reduction strategies
Timeframe	Up to 31 August 2024
Inclusion criteria	Original articles, narrative and systematic reviews, meta-analyses, consensuses and medical society guidelines published in English. The references included in these documents were scrutinized to identify any that could be relevant to the review
Selection process	The articles were selected by the author. All the articles were meticulously reviewed for inclusion in the review

LILACS, Latin American and the Caribbean Literature on Health Sciences.

gene *CHEK2*, found on chromosome 22q12.1, encodes the serine/threonine-protein kinase checkpoint kinase 2 (Chk2), which is activated by the *ATM* protein in response to DNA damage, particularly double-stranded DNA breaks (18). Associations have been described between *CHEK2* PVs and an increased risk of female BC (5,6,13,16,19-24). Furthermore, there have been reports of an increased risk of colorectal cancer (21,25,26), prostate cancer (21,27,28), kidney cancer (13,29,30), thyroid cancer (13,31), and hematological cancers (32) in *CHEK2* PV carriers. A positive association has also been reported between *CHEK2* PVs and the risk of male BC (19,33-37). However, one of the most consistent associations of *CHEK2* PVs is with female BC, which tends to develop at an earlier age (13,38-41).

As a moderate-penetrance susceptibility gene, *CHEK2* increases the risk of BC approximately 2-3-fold (5,6,16,42). That risk is multifactorial, involving family history (21,41-46), breast density, lifestyle characteristics (41), and genotype (6,13,44). Polygenic risk scores can refine risk prediction in *CHEK2* PV carriers (41,47-49).

Considering the relevance and timeliness of this topic, a narrative review was performed to investigate various aspects of the relationship between *CHEK2* PVs and BC. Current evidence and its implications for counseling and managing *CHEK2* PV carriers are discussed. I present this article in accordance with the Narrative Review reporting checklist (available at https://tbcr.amegroups.com/article/view/10.21037/tbcr-24-53/rc).

Methods

A comprehensive literature search was performed using the PubMed, Embase, Google Scholar and Latin American and the Caribbean Literature on Health Sciences (LILACS) databases up to August 31, 2024. *Table 1* details the research strategy.

Findings and discussion

Frequency of CHEK2 PVs and associated BC risk

The frequency of *CHEK2* PVs differs among populations and ethnic groups (6,12,14,17,42,50-57). Initial studies concentrated on *CHEK2* c.1100del, a protein-truncating variant. Subsequently, full *CHEK2* gene sequencing identified new variants.

Early reports on *CHEK2*-associated BC identified the c.1100del variant in 55/1,071 (5.1%) of *BRCA1/2*-negative BC patients and in 18/1,620 (1.1%) of controls (P=0.00000003) (19). In a meta-analysis of 16 prospective cohort and case-control studies (26,488 cases and 27,402 controls), the c.1100del variant led to an increased risk of BC in unselected patients [odds ratio (OR): 2.7; 95% confidence interval (CI): 2.1–3.4], in early-onset BC (OR: 2.6; 95% CI: 1.3–5.5) and familial BC (OR: 4.8; 95% CI: 3.3–7.2) (58). The cumulative risk in women with a family history of BC was 37% at 70 years (58). In a later meta-analysis of 25 case-control studies (29,154 cases and 37,064 controls), the frequency of the c.1100del variant was 1.34%

in BC patients and 0.44% in controls (59). The c.1100del variant led to an increased risk of BC (OR: 2.75; 95% CI: 2.25–3.36), familial BC (OR: 3.72; 95% CI: 2.61–5.31) and early-onset BC (OR: 2.78; 95% CI: 2.28–3.39) (59). In another meta-analysis of 26 case-control studies (118,735 BC patients and 195,807 controls), the c.1100del variant conferred an overall increased risk of BC (OR: 2.89; 95% CI: 2.63–3.16) and of female BC (OR: 2.88; 95% CI: 2.63–3.16) (60). Other meta-analyses have reported a significant association of *CHEK2* c.1100del (OR: 3.10; 95% CI: 2.59–3.71), p.I157T (OR: 1.52; 95% CI: 1.31–1.77) (61) and protein-truncating variants (OR: 3.25; 95% CI: 2.55–4.13) (22) with BC risk.

A study conducted in Poland with 7,496 *BRCA1*-negative women with BC and 4,346 controls, identified a *CHEK2* protein-truncating variant (del5395, IVS2+1G>A, c.1100del) in 3.0% of the cases and in 0.8% of the controls (44). Conversely, the missense variant p.I157T was found in 7.1% of cases and in 4.9% of controls (44). The lifetime BC risk in *CHEK2* protein-truncating variant carriers was 20% for women with no family history of BC and 34% for those with one first-degree relative affected (44). A Dutch study reported a significant increase in BC risk in women from c.1100del families [standardized incidence ratio (SIR): 4.88; 95% CI: 4.62–5.16], with this risk being significant from 25 years of age onwards (SIR: 19.94; 95% CI: 13.14–29.01) (32).

In a Brazilian study conducted with 207 *CHEK2* variant carriers, 96 PVs and 111 with variants of uncertain significance (VUS), the most common variants were: p.Arg117Gly (14.5%), p.I157T (7.2%) and c.1100del (6.7%). BC was the phenotype in 76.7% (23/30), 57.1% (8/14) and 33.3% (5/15) of the p.Arg117Gly, c.1100del and p.I157T variant carriers, respectively (62). Likewise, in another Brazilian study with 1,663 BC patients, the frequency of *CHEK2* PVs was 1.32%, with p.Arg117Gly or p.R117G being the most commonly found variant, corresponding to around one-third of PVs in this gene (8). The missense variant p.R117G is associated with a significant increase in BC risk, with reported ORs of 2.26 (95% CI: 1.29–3.95) (63), 2.69 (95% CI: 1.46–4.94) (64) and 2.95 (95% CI: 1.85–4.71) (65). A Chinese study involving 8,067 women with BC and 13,129 controls found *CHEK2* PVs in 0.32% of cases and 0.13% of controls, significantly increasing BC risk (OR: 2.5; 95% CI: 1.4–4.6) (14). Another Chinese study involving 7,657 *BRCA1/2*-negative BC patients and no control group reported a frequency of *CHEK2* PVs of 0.34% (66).

In two large case-control studies, *CHEK2* PVs were significantly associated with BC risk. In the Cancer Risk Estimates Related to Susceptibility Genes (CARRIERS) study, the absolute risk of BC exceeded 20% at 85 years of age for women with *CHEK2* PVs (5). In the Breast Cancer Risk after Diagnostic Gene Sequencing (BRIDGES) study, for women with *CHEK2* protein-truncating variants, the absolute risk of BC at 80 years of age was 17–30% (6). Similarly, in the Electronic Medical Records and Genomics (eMERGE) III Network, the cumulative risk of BC in women with *CHEK2* PV was 23.6% (95% CI: 19.4–27.8%) by 70 years of age (11). Boddicker *et al.* (67) reported a remaining lifetime risk of BC of 14.9% (95% CI: 10.8–20.7%) in women aged 66–85 years with *CHEK2* PV. In a population-based, case-control family study conducted in Australia with 1,476 cases and 861 controls, the cumulative BC risk in women with *CHEK2* PVs ranged from 2.6% (95% CI: 1.45–5.1%) at 40 years of age to 33% (95% CI: 21–48%) by 80 years of age (12). That study included twelve c.1100del and six p.Arg117Gly carriers (12). The frequency of *CHEK2* PVs and the estimated BC risk in different populations are shown in *Table 2*.

Evidence shows differences in the overall frequency of *CHEK2* PVs and of specific variants across populations. To analyze the pathogenicity of *CHEK2* variants in general, one of the procedures reported was to compare findings of the studies with those of ClinVar (15,68) or adopt the pathogenicity assigned in ClinVar (5,12). The American College of Medical Genetics and Genomics (ACMG) guidelines (69) were used in some of the studies (8,10,11,13-15,68). While some authors performed targeted-sequencing of the coding regions of the *CHEK2* gene, others investigated specific variants. Another strategy used was to confirm PVs using Sanger sequencing (11,15). Some investigators described the variants identified (8,12,15,34,68). In most studies, BC risk was analyzed for all the PVs combined, and that prevented reporting the risk for each variant. However, considering the low frequencies, it does not appear feasible to calculate the BC risk for each variant, except for the most common ones such as c.1100del and p.I157T. The magnitude of the association between *CHEK2* PVs and BC risk varies, particularly according to family history and PV type. There is robust evidence that *CHEK2* protein-truncating variants confer a greater risk of BC than missense variants. Further studies are required to estimate the absolute risk of BC in *CHEK2* missense variant carriers. Whenever possible, the risk associated with each individual variant is described in this review.

Table 2 Frequency and estimates of breast cancer risk, when available, in *CHEK2* pathogenic variant carriers

Reference	Country	Study design	Population	Age (years)	Main findings, n (%)
Hu *et al.*, 2021 (5)	USA	Population-based case-control	Women • Cases: 32,247 • Controls: 32,544	Cases: 62.07 Controls: 61.22	Cases: 349 (1.08%) Controls: 138 (0.42%) OR: 2.47; 95% CI: 2.02–3.05
Dorling *et al.*, 2021 (6)	Countries in different continents	Population-based case-control	Women • Cases: 47,522 • Controls: 50,475	Cases: 54.4 Controls: 54.62	Protein-truncating variants Cases: 704 (1.48%) Controls: 315 (0.62%) OR: 2.54; 95% CI: 2.21–2.91
Ahearn *et al.*, 2022 (53)	Ghana	Population-based case-control	Women • Cases: 871 • Controls: 1,563	Cases: 50.8 Controls: 45.8	Cases: 0 Controls: 1 (0.06%)
Kim *et al.*, 2017 (54)	South Korea	Prospective	235 BRCA1/2-negative BC patients	Age of *CHEK2* PV carriers at BC diagnosis: 33	1 (0.40%)
Nguyen-Dumont *et al.*, 2021 (12)	Australia	Population-based case-control-family	Women • Cases: 1,476 • Controls: 861	≤40	Cases: 20 (1.4%) Controls: 7 (0.8%) Hazard ratio: 4.9; 95% CI: 2.5–9.5
Fu *et al.*, 2022 (14)	China	Case-control study	Women • Cases: 8,067 • Controls: 13,129	Cases: 50 Controls: 33	Cases: 26 (0.32%) Controls: 17 (0.13%) OR: 2.5; 95% CI: 1.4–4.6
Krivokuca *et al.*, 2022 (55)	Serbia	Retrospective	392 patients with BC and/or ovarian cancer	Median age at cancer diagnosis: 40 (range, 21–67)	15 (3.8%)
Kasugai *et al.*, 2022 (56)	Japan	Hospital-based case-control	Women • Cases: 629 • Controls: 1,153	Median Cases: 52 Controls: 52.3	Cases: 1 (0.16%) Controls: 0 OR: 4.24; 95% CI: 0.17–107.27
Bora *et al.*, 2022 (57)	Turkey	Retrospective	419 BC patients	Median age at BC diagnosis: 44 (range, 22–87)	18 (4.3%)
Guindalini *et al.*, 2022 (8)	Brazil	Laboratory-based study. Case-control analysis	Cases: 1,663 BC patients (99.2% women) Brazilian reference controls: 18,919	Mean age at BC diagnosis: 42.9±11.2	22 (1.32%)
Öfverholm *et al.*, 2023 (15)	Sweden	Retrospective	4,013 BC women	Median age at first diagnosis of BC: 45	Only protein-truncating variants 147 (3.66%)

BC, breast cancer; CI, confidence interval; OR, odds ratio; PV, pathogenic variant.

CHEK2 variants with conflicting pathogenicity classifications

There are currently 197 *CHEK2* variants with conflicting classifications of pathogenicity in ClinVar (70). Here, three of these variants, all missense, are discussed: p.I157T, p.S428F and p.T476M.

In ClinVar, the *CHEK2* c.470T>C (p.I1e157Thr) or p.I157T variant may be found as pathogenic; likely pathogenic; pathogenic, low penetrance; established risk allele; risk factor; and VUS (70). In a Finnish case-control study involving 1,035 unselected BC patients and 1,885 controls, the frequency of the p.I157T variant was 7.4% for cases and 5.3% for controls (71). Furthermore, p.I157T was associated with an increased overall risk of BC (OR: 1.38; 95% CI: 1.03–1.83) and of unselected BC (OR: 1.43; 95% CI: 1.06–1.95) (71). In a Polish study with 7,782 BC patients and 6,233 controls, p.I157T was identified in 7.7% of BC patients and 5.1% of controls (72). In that study, women with *CHEK2* protein-truncating variants had a higher BC risk (OR: 3.3; 95% CI: 2.4–4.3) compared to carriers of the p.I157T missense variant (OR: 1.6; 95% CI: 1.4–1.9) (72). A later meta-analysis of 15 case-control studies totalizing 19,621 cases and 27,001 controls showed the p.I157T variant to be associated with an increased risk of unselected female BC (OR: 1.48; 95% CI: 1.31–1.66); familial BC (OR: 1.48; 95% CI: 1.16–1.89); and early-onset BC (OR: 1.47; 95% CI: 1.29–1.66) (73). In another meta-analysis of eight case-control studies involving 15,985 cases and 18,609 controls, the p.I157T variant was associated with an increased risk of BC (OR: 1.58; 95% CI: 1.42–1.75) (26). The conflicting pathogenicity classifications of the p.I157T variant are likely due to the strong evidence that the OR for BC is less than 2-fold, i.e., below the level set to define actionability (74).

The *CHEK2* c.1283C>T (p.Ser428Phe) or p.S428F variant is classified in ClinVar as pathogenic; likely pathogenic; pathogenic, low penetrance; established risk allele; and VUS (70). In a retrospective study with Ashkenazi Jews, the p.S428F variant was identified in 2.88% (47/1,632) of BC patients unselected for family history of BC and in 1.37% (23/1,673) of controls. The p.S428F carriers had an increased risk of BC (OR: 2.13; 95% CI: 1.25–3.63) (75). However, in a study with a larger sample size, the frequency of p.S428F in Ashkenazi Jewish women with BC was 2.52% (162/6,420) compared to 2.01% (47/2,335) in the controls and was unassociated with any increased risk of BC (OR: 1.25; 95% CI: 0.90–1.74) (76).

The *CHEK2* c.1427C>T (p.Thr476Met) or p.T476M variant is classified in ClinVar as pathogenic; likely pathogenic; established risk allele; and VUS (70). In a retrospective laboratory-based study conducted in the US with 2,580 individuals with *CHEK2* PVs (93.3% women), the most common cancers were female BC (59.9%), prostate cancer (20.1%) and male BC (11.8%) (10). The most common PVs were c.1100del (30.8%), p.I157T (27.3%), p.S428F (8.0%) and p.T476M (5.3%). Compared to the frequency of BC in c.1100del carriers (65%), women with p.I157T (52.4%; P=0.0004) or p.S428F variants (42.2%; P=0.0004) had significantly less BC; however, there was no statistically significant difference in relation to p.T476M carriers (55.0%; P=0.07) (10).

Another laboratory-based study included 3,783 participants (92% women) with *CHEK2* PVs. The four most common PVs were c.1100del (n=1,252), p.I157T (n=992), p.S428F (n=324) and p.T476M (n=250) (13). BC was significantly less common in carriers of p.I157T (OR: 0.66; 95% CI: 0.56–0.78) and p.S428F (OR: 0.59; 95% CI: 0.46–0.76) compared to carriers of other PVs. This was not the case for p.T476M carriers (13). The frequency of BC was similar when p.I157T, p.S428F and p.T476M carriers were compared with non-carriers (13). In some studies, the p.I157T, p.S428F (5,13,15,68,77) and p.T476M (13) variants were excluded from the analyses or analyzed separately.

A finding of *CHEK2* p.I157T, p.S428F and p.T476M variants at MGPT is not uncommon, particularly in populations of European ancestry. Evidence shows that the p.I157T and p.S428F variants are associated with a lower BC risk compared to the c.1100del variant. The conflicting categories of pathogenicity are challenging, particularly when the same variant is classified as VUS and pathogenic. This hampers counseling and can result in different forms of management (78). Categories such as pathogenic, low risk; risk factor; and established risk allele are unclear for clinical practice. The management of *CHEK2* PV carriers cannot rely solely on the genetic variant. Other factors, at the very least family history, should also be considered (44,79).

Monoallelic and biallelic CHEK2 variants

The phenotype of biallelic variants in tumor-suppressor genes usually differs from that of monoallelic variants (80). A recessive phenotype of the *CHEK2* gene is not recognized (79). A woman homozygous for the c.1100del variant was reported to have bilateral BC and a uterine sarcoma (50). In a later Polish study involving 7,782 women with BC and

6,233 controls, carriers of two *CHEK2* PVs (22 cases) had a higher risk of BC (OR: 3.9; 95% CI: 1.5–10) compared to women with one variant (807 cases) (OR: 1.9; 95% CI: 1.6–2.1) (72). The women who were homozygous for the p.I157T variant (13 cases) were not found to have any significant risk of BC (72).

In a Dutch cohort of *BRCA1/2*-negative women with familial BC, heterozygosity and homozygosity for the c.1100del variant were found in 112/2,554 (4.4%) and 8/2,554 (0.3%) of women with BC, respectively (81). The risk of BC for women who were homozygous for the c.1100del variant was twice that of women who were heterozygous (81), as also suggested in another study with six women with BC who were homozygous for the c.1100del variant (82). However, in both studies the number of homozygous participants was small, with a wide CI range for the estimated BC risk (77,79).

Three US laboratory-based studies reported the association between biallelic *CHEK2* PVs and the risk of BC (10,13,77). In the first, 6,473 monoallelic and 31 biallelic women with *CHEK2* PVs were included (77). The p.I157T and p.S428F variants were classified as VUS and were excluded from the analysis. Compared to monoallelic carriers, biallelic carriers had a higher rate of BC (80.6% versus 41.2%, respectively; P<0.0001) and were more likely to be diagnosed at ≤50 years of age (61.3% versus 23.9%, respectively; P<0.0001) and to develop a second primary BC (22.6% versus 8.1%, respectively; P=0.0107) (77). Furthermore, biallelic PV carriers have ORs of 8.69 (95% CI: 3.69–20.47) and 4.98 (95% CI: 2.00–12.35) for developing invasive BC and ductal carcinoma *in situ*, respectively (77). In the second study, *CHEK2* PVs were identified in 2,508 individuals (93.3% women), with 32 of these (1.3%) being biallelic carriers (10). There was no statistically significant difference in the prevalence of BC (male or female) or in age at diagnosis of female BC between biallelic and monoallelic *CHEK2* PV carriers (10). In the third study, BC was more common in biallelic carriers (n=20; 95.2%) compared to monoallelic (n=1,339; 67.1%) and to non-carriers (n=16,029; 52.7%) (P<0.001 for both comparisons) (13). Biallelic *CHEK2* PV carriers were diagnosed with BC at a younger age compared to monoallelic carriers (40 versus 47 years, respectively; P=0.02) and non-carriers (40 versus 50 years, respectively; P=0.001) (13). The p.I157T, p.T476M and p.S428F variants were of low risk and excluded from the analyses (13). Rainville *et al.* reported similar findings (77).

In a Swedish study involving 4,622 women with breast and/or ovarian cancer, 765 (16.6%) had at least one PV. Seven women had biallelic *CHEK2* PVs (0.15%), with six of these having bilateral BC (15). Interestingly, in the study with the largest cohort of biallelic *CHEK2* PV carriers to date, which included 294 individuals (210 women), the type of mutation [loss-of-function (LOF) versus missense] affected the cancer phenotype (83). BC was more common in women with biallelic LOF PVs compared to women who were homozygous for the p.I157T variant (94.6% versus 71.7%, respectively; P<0.05). BC developed at a younger age in women with biallelic LOF *CHEK2* PVs (43.5 years) compared to women who were homozygous for p.I157T (51 years; P<0.05) and those with monoallelic LOF *CHEK2* PVs (49 years; P=0.0015) (83).

Most evidence suggests a severe cancer phenotype for biallelic *CHEK2* PV carriers, with a greater frequency of BC, multiple BCs and early-onset BC compared to monoallelic *CHEK2* PV carriers.

Male BC

In men, the average lifetime risk of BC is around 1 in 726 (84). High penetrance BC susceptibility genes are currently assessed in all cases of male BC (9,85). *CHEK2* is usually included in the MGPT. The frequency of *CHEK2* PVs in male BC differs according to the population studied (34,36,86-90).

In a British study conducted with 204 families with at least one case of male BC, 51 had PVs in *BRCA2* (25%) and 5 had PVs in *CHEK2* (2.45%) (91). A retrospective laboratory study in the US found that the frequency of *CHEK2* PVs was 4.1% (16/386) in male BC patients (34). All *CHEK2* PVs (c.591delA, p.R117G, c.1100del, p.T476M, p.I157T, p.S428F, p.Q29*) and the c.1100del variant were associated with a risk of male BC, with ORs of 2.43 (95% CI: 1.4–3.9) and 3.8 (95% CI: 1.7–7.8), respectively (34). In a retrospective German study, *CHEK2* PVs were the most common variants (11/340, 3.2%) in men with *BRCA1/2*-negative BC (36). Furthermore, CHEK2 protein-truncating variants were associated with a risk of male BC (OR: 3.78; 95% CI: 1.57–7.71) (36). Other studies (19,32,33,35,92,93), including a systematic review (37) and a meta-analysis of the c.1100del variant (OR: 3.13; 95% CI: 1.94–5.07) (60), reported a positive association between *CHEK2* PVs and a risk of male BC.

Conversely, *CHEK2* PVs were not identified in a cohort of 81 male BC patients in Italy (87) or in another of 85 patients in France (90). In an Italian case-control study involving 767 male BC patients and 2,512 controls, the

frequency of *CHEK2* PVs was 0.4% in the cases and 0.3% in the controls (89). No statistically significant association was found between *CHEK2* PVs and the risk of male BC (OR: 1.40; 95% CI: 0.35–5.63) (89). Other investigators have also failed to find any association (94-96).

Overall, evidence suggests that *CHEK2* PVs increase the risk of male BC, particularly in protein-truncating variant carriers. Data remain insufficient on the reduced risk and BC surveillance in men with *CHEK2* PV. Men with *CHEK2* protein-truncating variants should be counseled to self-examine their breasts and be made aware of symptoms (79).

Pathologic characteristics of the tumor

A positive relationship between *CHEK2*-associated BC and invasive lobular carcinoma (ILC) has been described (44,46,97-101). However, other studies did not corroborate that association (102-104). In the CARRIERS study, two large cohorts were evaluated. One population-based cohort consisted of 2,999 women with ILC; 20,323 with invasive ductal carcinoma (IDC); and 32,544 unaffected controls. The other was a clinical cohort with 3,796 women with ILC; 37,405 with IDC; and controls from the genome aggregation database (gnomAD) (101). *CHEK2* PVs increased the risk of ILC both in the population-based (OR: 2.56; 95% CI: 1.71–3.73) and clinical cohorts (OR: 2.01; 95% CI: 1.34–2.90). However, the p.I157T variant was associated with a risk of ILC in the population-based cohort (OR: 1.76; 95% CI: 1.18–2.54) but not in the clinical cohort (OR: 1.29; 95% CI: 0.79–1.97) (101).

Conversely, in a meta-analysis (717 cases and 13,842 controls), the risk of ILC in p.I157T carriers was more than twice (OR: 4.17; 95% CI: 2.89–6.03) (73) that reported in the CARRIERS study (101), albeit with a smaller sample. The p.I157T variant was not associated with a risk of ILC in British women (1,434 cases of ILC and 1,611 controls) (46). Nevertheless, an association was found between *CHEK2* PVs and a risk of ILC (OR: 4.31; 95% CI: 1.61–11.58) and, more strongly, a risk of lobular carcinoma *in situ* (OR: 9.90; 95% CI: 3.42–28.66) (46). Other authors found no association between *CHEK2* PVs and a risk of ILC in smaller cohorts (103,104).

Regarding hormone receptors, cases of *CHEK2*-associated BC are more likely to express estrogen receptors (ER) compared to *CHEK2*-negative cases (5,6,13,14,39,40,99,100,105-110). The BRIDGES study evaluated 42,680 female BC patients and 46,387 controls and found that *CHEK2* protein-truncating variants were associated with almost all subtypes of BC, including hormone receptor-negative and ERBB2-positive (OR: 2.21; 95% CI: 1.41–3.48) but not triple-negative breast cancer (TNBC) (OR: 1.25; 95% CI: 0.81–1.94) (111). Furthermore, *CHEK2* protein-truncating variants (around 80% being c.1100del) were associated with larger tumors, a greater likelihood of lymph node involvement and a more advanced stage at diagnosis (111). In the CARRIERS study, *CHEK2* PVs increased the risk of ER-positive BC (OR: 2.60; 95% CI: 2.05–3.31) but not of ER-negative BC (OR: 1.40; 95% CI: 0.83–2.25) or TNBC (OR: 1.63; 95% CI: 0.72–3.20) (5). Likewise, in a cohort of 1,514 British women with TNBC, the c.1100del variant was not linked to this subtype (112).

In a cohort of 7,496 Polish women with BC who tested negative for *BRCA1* (10.2% had *CHEK2* PV), *CHEK2*-related cases were significantly more likely to express ER (69.7% versus 63.1% in *CHEK2*-negative cases; P=0.002) and progesterone receptors (PR) (77.0% versus 68.7%, respectively; P<0.001) and to involve the lymph nodes (51.0% versus 45.5%, respectively; P=0.02). However, there was no association with tumor size (44). In the Breast Cancer Association Consortium, women with BC and *CHEK2* p.I157T or c.1100del variants were more likely to have tumors of the luminal A or B subtypes compared to non-carriers (100). In that study, ILC and grade 1 tumors were more common in p.I157T carriers (22.0% and 26.7%, respectively) compared to c.1100del carriers (14.3% and 17.4%, respectively) and non-carriers (15.3% and 22.5%, respectively). Cases of TNBC were notably more common in non-carriers (14.2%) compared to p.I157T (6.2%) or c.1100del variant carriers (3.6%). There was no difference in tumor size or axillary status between *CHEK2* PV carriers and non-carriers (100). Likewise, Rhiem *et al.* (113) reported three cases (0.2%) of *CHEK2* PV and Couch *et al.* (114) found no cases in 1,600 and 1,824 women with TNBC, respectively.

The Prospective Study of Outcomes in Sporadic versus Hereditary BC (POSH) evaluated 2,344 British women with BC diagnosed at ≤40 years of age (68). *CHEK2* protein-truncating variant (c.1100del, c.1263del, c.283C>T, c.405del, c.409C>T, c.444+1G>A, c.58C>T, c.655del) carriers were significantly more likely to have grade 2 tumors (53.8% versus 36.0% in non-carriers; P=0.029); be ER-positive (88.7% versus 68.3%, respectively; P=0.0016); be PR-positive (78.6% versus 58.7%, respectively; P=0.0094); and have lymph node involvement (69.8% versus 51.9%, respectively; P=0.0098); and less likely to have TNBC (1.9% versus 18.2%, respectively; P=0.0022).

There was no association between *CHEK2* PVs and tumor size at baseline and ERBB2 status (68). An association was also found between *CHEK2*-related BC and grade 2 (92,102) but not with tumor stage or size at diagnosis (92,100,102,115,116).

Overall, *CHEK2* PVs were positively associated with ER-positive, grade 1/2 tumors, and with a lower risk of TNBC. A strong association was found between *CHEK2* PVs and a risk of ILC. Findings on lymph node involvement, tumor size and stage at diagnosis differ. At least partially, these discrepancies could be due to differences between populations and study designs.

Risk of contralateral BC (CBC)

The risk of CBC is approximately 0.4% per year in the general population of BC patients (117-119). The risk is multifactorial, involving family history (120,121), ER-status of the primary BC, body mass index, chemotherapy, endocrine therapy (117,121), histologic type (121), and PV in BC predisposition genes (119,121).

The Women's Environmental, Cancer and Radiation Epidemiology (WECARE) study evaluated 1,395 women with unilateral BC and 708 with CBC. The c.1100del variant was not associated with a risk of CBC [relative risk (RR): 1.8; 95% CI: 0.6–5.4] (122); however, the small number of c.1100del carriers (7/708, 1.0%) hampered that analysis. Conversely, a retrospective analysis of 4,722 women with BC in the Netherlands found that c.1100del carriers (4.1%) had an increased risk of CBC [hazard ratio (HR): 3.97; 95% CI: 2.59–6.07] compared to non-carriers (115). With a weaker association, other researchers reported that *CHEK2* PVs (excluding the p.I157T variant) and c.1100del variant carriers had an increased risk of CBC, with ORs of 1.81 (95% CI: 1.42–2.28) and 1.84 (95% CI: 1.34–2.47), respectively (123).

In the POSH study, women with early-onset BC who were *CHEK2*-negative had 5- and 10-year rates of CBC of 2.7% and 3.7%, respectively (68). Conversely, in *CHEK2* protein-truncating variant carriers, these rates were 7.5% and 9.4%, respectively (68). In the CARRIERS study, 15,104 women with BC were evaluated prospectively, with carriers of *CHEK2* protein-truncating variants being found to have an increased risk of overall CBC (HR: 1.9; 95% CI: 1.1–3.3) and ER-positive CBC (HR: 2.0; 95% CI: 1.1–3.5) (119). The 10-year cumulative incidence of CBC was 4.3% (95% CI: 3.9–4.6%) for women without PV and 7.9% (95% CI: 4.1–15.0%) for *CHEK2* protein-truncating variant carriers. In women with *CHEK2* PV, this incidence was 13.2% (95% CI: 6.0–29.3%) before menopause and 4.3% (95% CI: 1.4–13.3%) after menopause (119). The p.I157T variant was not associated with a risk of CBC (HR: 1.3; 95% CI: 0.5–3.4) (119).

In another study with 30,628 women with BC, 676 cases of CBC occurred, with 103 of these women being carriers of some BC predisposition gene (124). In the adjusted multivariate analysis, *CHEK2* protein-truncating and c.1100del variants were associated with an increased risk of CBC, with HRs of 2.25 (95% CI: 1.55–3.27) and 2.43 (95% CI: 1.63–3.62), respectively. The 10-year cumulative incidence of CBC was 6.7% in *CHEK2* protein-truncating variant carriers (124). With varying strengths of association, other studies with female *CHEK2* PV carriers (13,39,125,126), including a meta-analysis of c.1100del carriers (RR: 2.68; 95% CI: 1.96–3.65) (121), reported an increased risk of CBC. Nonetheless, the evidence does not show that radiotherapy increases the risk of CBC in women with *CHEK2*-related BC (122,127,128).

The body of evidence indicates an increased risk of CBC in *CHEK2* PV carriers compared to non-carriers. The magnitude of this risk varies and appears to be variant-specific, being particularly associated with protein-truncating variants such as c.1100del.

Survival

Findings are conflicting regarding the impact of *CHEK2* PVs on BC survival. In a cohort of women with BC followed up for a median of 6.6 years, Weischer *et al.* (39) reported that c.1100del carriers had a greater risk of early death compared to non-carriers when considering the overall cohort (HR: 1.47; 95% CI: 1.22–1.76) and the ER-positive cases (HR: 1.43; 95% CI: 1.12–1.82) but not the ER-negative cases (HR: 0.95; 95% CI: 0.52–1.74). Likewise, c.1100del carriers had a greater risk of BC-specific death compared to non-carriers in the overall cohort (HR: 1.66; 95% CI: 1.36–2.04), in the ER-positive cases (HR: 1.63; 95% CI: 1.24–2.15) but not in the ER-negative cases (HR: 1.09; 95% CI: 0.56–2.14) (39).

A Polish study investigated survival in 3,105 *CHEK2*-negative and 487 *CHEK2* PV carriers (c.1100del, IVS2+1G>A, del5395, p.I157T) followed up for a mean of 8.9 years (106). Contrary to the findings of Weischer *et al.* (39), there was no difference in survival between *CHEK2* PV (any) (HR: 1.14; 95% CI: 0.90–1.44), p.I157T (HR: 1.24; 95% CI: 0.96–1.61) and *CHEK2* protein-truncating variant carriers (HR: 0.87; 95% CI: 0.55–1.39) compared to non-carriers (106).

Furthermore, in women with ER-positive BC, the *CHEK2* protein-truncating variant did not affect survival (HR: 0.86; 95% CI: 0.48–1.55); however, survival was poorer in p.I157T carriers (HR: 1.53; 95% CI: 1.10–2.14) (106). Other authors failed to find any association between *CHEK2* PVs and survival in women with BC (44) or between ER-status in *CHEK2* PV carriers and survival (115,124).

In the POSH study, with a median follow-up of 8.2 years, women with *CHEK2* protein-truncating variants and BC had poorer overall survival (HR: 1.65; 95% CI: 1.05–2.59) and distant disease-free survival (HR: 1.60; 95% CI: 1.04–2.46) compared to *CHEK2*-negative women (68). A retrospective Dutch study found poorer BC-specific survival (HR: 2.05; 95% CI: 1.41–2.99) and distant disease-free survival (HR: 2.65; 95% CI: 1.79–3.93) in c.1100del carriers six years after BC diagnosis (115). Other investigators have reported a poorer BC prognosis in *CHEK2* PV carriers (126,129).

A prospective Polish study compared survival outcomes between 839 women with BC who carried *CHEK2* PV (c.1100del, IVS2+1G>A, del5395, p.I157T) and 839 women with BC who did not carry these variants (130). The 15-year survival rates were 76.6% and 78.8%, respectively (HR:1.06; 95% CI:0.84–1.34). Among *CHEK2* PV carriers, the 15-year survival rates were 86.3% for those who underwent oophorectomy compared to 72.1% for those who did not (HR: 0.59; 95% CI: 0.38–0.90) (130). Some studies have reported an association between *CHEK2* PVs and ovarian cancer risk (92,131), while others have found no such link (13,29,132,133). Current guidelines do not recommend surveillance or risk-reducing surgery for ovarian cancer in *CHEK2* PV carriers (9,134-136). Oophorectomy is not routinely recommended for *CHEK2* PV carriers, either as part of BC treatment or as a risk-reducing measure for ovarian cancer.

Data suggest that *CHEK2* PVs may negatively affect the survival of women with BC, varying according to PV type and ER-status. Nevertheless, these findings are inconclusive when bearing in mind the design of many of these studies. Further prospective studies with longer follow-up periods are required. Different variables associated with survival in women with BC, including treatment-related variables, should be considered.

The challenge of management

The multiple factors that affect BC risk make the management of women with *CHEK2* PV challenging. PVs in *CHEK2* are inherited in an autosomal-dominant pattern, with a 50% chance of transmission to offspring. Cascade testing of family members who could have inherited a PV should be recommended. Here, the management of women with *CHEK2* PVs is separated into unaffected or healthy women and women affected by BC.

Unaffected women

The management of women with *CHEK2* PV unaffected by BC should take at least genotype and family history of BC into account (44). The American College of Radiology recommends that female carriers of PV in BC susceptibility genes be submitted to annual breast magnetic resonance imaging (MRI) beginning at 25–30 years of age, with annual digital mammograms, with or without tomosynthesis, starting at 30 years of age (137). Age at initiation of mammography can be delayed to 40 years if MRIs are performed annually from 25 years onwards (137). Using a comparative modeling study, Lowry *et al.* (138) reported that annual breast MRI beginning at 30 or 35 years of age, followed by annual mammograms from 40 to 74 years of age reduced BC mortality by 57.0% (56.3–57.7%) to 58.4% (57.2–59.6%) in *CHEK2* PV carriers, respectively.

Table 3 lists guidelines for the management of healthy women with *CHEK2* PV as issued by the US National Comprehensive Cancer Network (NCCN) (9); the European Society for Medical Oncology (ESMO) (134), the UK Cancer Genetics Group (135) and eviQ in Australia (136). In general, these guidelines focus on breast awareness and a personalized evaluation of BC risk. Some protocols (79,134-136) suggest the use of specific tools, such as CanRisk, for calculating BC risk (139), including for carriers of *CHEK2* protein-truncating variant (139). Furthermore, mammography and MRI are recommended to monitor female *CHEK2* PV carriers (9,134-136). The ACMG (79) and the American Society of Clinical Oncology (ASCO) (140) guidelines state that the *CHEK2* p.I157T and p.S428F variants alone do not require breast surveillance; however, genotype and family history should also be taken into consideration in such cases (44,79,140).

Although risk-reducing mastectomy (RRM) is not routinely recommended for *CHEK2* PV carriers (9,141-144), it can be considered under certain circumstances such as with biallelic c.1100del (142), a family history of BC (first- or second-degree relatives) (9,141,142) or high-risk cases, calculated using tools such as CanRisk (79,135,136). At the 18th St. Gallen International BC Consensus, most of the panel voted in favor of intensive screening for pre- and

Table 3 Management of women with *CHEK2* pathogenic variants and unaffected by breast cancer

Strategy	NCCN (Version 3.2024) (9)	ESMO (134)	UK Cancer Genetics Group (135)	eviQ-Australia (136)		
				Age (years)	Moderate risk	High-risk
Surveillance	Annual MG starting at age 40 years and breast MRI to be considered starting at age 30–35 years[†]	Truncating variants: broad evaluation, including risk factors such as family history for the addition of MRI to MG from 40 years of age. Use of risk evaluation tools such as CanRisk	Moderate risk (LTR of 17–29%): annual MG 40–49 years, then NHSBSP High risk (LTR of ≥30% but <40%): annual MG 40–59 years, then NHSBSP		LTR from age 20 years: ≥17% but <30%. Risk between ages 40 and 50 years: 3–8%	LTR from age 20 years: ≥30%. Risk between ages 40 and 50 years: >8%
			Very high risk (LTR of ≥40% and a 10-year risk of 8% at ages 25–29 years and 30–39 years, or 12% at 40–49 years): annual breast MRI from age 30 years and annual MG from age 40 years	<40	No routine screening recommended	Evaluate 10-year breast cancer risk using tools such as CanRisk or iPrevent. Age at initiation of screening should be individualized if the 10-year risk is ≥3%. Annual breast MRI to be performed if screening is recommended
			Biallelic *CHEK2* carriers (truncating variants): very high-risk screening to be recommended	40–50	Annual MG; annual breast MRI to be considered in case of dense breasts	Annual breast MRI; annual MG; tomosynthesis to be considered
				>50	MG every two years; annual MG to be considered if additional risk factors are present; other imaging modalities may be considered	Annual MG; tomosynthesis to be considered; annual breast MRI to be considered in case of dense breasts
Chemoprevention	Not stated	Not stated	To be considered according to family history of breast cancer		Premenopausal women from age 35 years: use of tamoxifen may be considered Postmenopausal women: use of raloxifene, aromatase inhibitors or tamoxifen may be considered	
Surgical	Evidence insufficient for RRM; management based on family history	Not stated	RRM to be considered if LTR ≥30%, together with risk evaluation using tools such as CanRisk		RRM is not recommended for women at moderate risk of breast cancer RRM to be discussed in cases of women at a high risk	

[†], can be modified based on family history (5–10 years prior to the youngest diagnosis in the family) or according to the specific variant. ESMO, European Society for Medical Oncology; LTR, lifetime risk; MG, mammogram; MRI, magnetic resonance imaging; NCCN, National Comprehensive Cancer Network; NHSBSP, National Health Service Breast Screening Programme; RRM, risk-reduction mastectomy.

post-menopausal *CHEK2* PV carriers, in the proportion of 71% and 79%, respectively. A proportion of 8% and 1.5% of the panel elected RRM for the pre-menopause and post-menopause, respectively (145). The woman's choice of whether to undergo intensive screening or RRM should be considered in a shared decision-making process.

No data are available on the efficacy of tamoxifen for the primary prevention of BC in *CHEK2* PV carriers (136,142). The eviQ and UK Cancer Genetics Group guidelines contemplate the use of chemoprevention in women with *CHEK2* PV (135,136), in line with the strong association between *CHEK2* PVs and ER-positive BC (5,6,13,40,110).

Preimplantation genetic testing for moderate-penetrance genes such as *CHEK2* is controversial and not usually recommended (79). There does not appear to be any contraindication to the use of the oral contraceptive pill (134,135), at least for a short period of time (146), taking its risks and benefits, as well as the other contraceptive options, into consideration (134-136). The use of hormonal contraception is contraindicated for users of tamoxifen due to the risk of venous thromboembolism (134). There are no data on systemic hormone therapy for menopausal *CHEK2* PV carriers. The use of low-dose vaginal estrogens for the relief of menopausal genitourinary symptoms can be considered (134), since they are effective and involve minimal systemic absorption (147).

Women affected by BC

The management of women with *CHEK2* PV and unilateral BC merits consideration. Regarding the surgical approach to the index BC, no randomized clinical trials were found comparing breast-conserving therapy (BCT) with mastectomy in women with *CHEK2* PV and BC. If, on the one hand, most of the outcomes are similar in *BRCA1/2* PV carriers with BC undergoing BCT or mastectomy (148), on the other hand, there are no data for women with *CHEK2* PVs. The risk of locoregional recurrence is greater for women with PVs in *BRCA1/2* and BC submitted to BCT compared to mastectomy (HR: 4.54; 95% CI: 2.77–7.42) (148). Considering these data, it can be hypothesized that most outcomes in *CHEK2* PV carriers with BC would be similar to those of non-carriers. However, there are no data on locoregional recurrence in women with BC and *CHEK2* PVs. According to ASCO, the American Society for Radiation Oncology, and the Society of Surgical Oncology guidelines, in patients with BC and PV in moderate-penetrance genes, BCT should be offered when this approach is appropriate (149,150). Up to now, there are no data indicating that the mutational state alters the local or systemic treatment of the index BC in *CHEK2* PV carriers (135,142).

When mastectomy is the treatment of choice, nipple-sparing mastectomy is a reasonable approach for women with BC and PV in moderate-penetrance genes (149), which include the *CHEK2* gene. When the treatment option for the index BC is BCT or unilateral mastectomy, intensive breast screening should be maintained (9,134,149). Regarding the risk of CBC, contralateral RRM is not recommended as routine (79). When deciding about contralateral RRM, the patient's age and family history (149,151) should be taken into consideration, while remembering that endocrine therapy can modify this risk, since many cases of *CHEK2*-related BC are ER-positive (151). Considering BC stage at diagnosis is important, since the prognosis can be determined by the primary BC. The decision regarding contralateral RRM should be shared with the patient, while highlighting the surgeon's role in the process (152).

Conclusions

Since PVs in *CHEK2* are commonly identified at MGPT, it is crucial for healthcare professionals to familiarize themselves with the subject and be able to provide adequate counseling and management of *CHEK2* PV carriers and their families.

Up to now, studies on *CHEK2* PVs have been conducted predominantly in cohorts of European ancestry. There is an urgent need for genetic diversity in such studies, particularly increasing the representation of individuals from Latin America, Africa and Asia. This could provide insights into the association between *CHEK2* PVs and the risk of BC.

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Footnote

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