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Population-based analysis of CHEK2 pathogenic variants and their functional role in breast cancer development

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CHEK2 is an essential tumor suppressor gene involved in DNA damage response and cell cycle regulation, and its germline variants are known to increase breast cancer susceptibility. However, evidence regarding the clinical and molecular relevance of CHEK2 variants in Central Asian populations remains limited. This study aimed to assess the distribution and clinicopathological significance of the CHEK2 IVS2+1G>A and Ile157Thr polymorphisms in Uzbek women with breast cancer, with emphasis on molecular subtypes, immunohistochemical markers, and menopausal status. The study included 200 breast cancer patients and 100 conditionally healthy controls. CHEK2 polymorphisms were identified using PCR-based genotyping. Associations with clinicopathological features and immunohistochemical markers (ER, PR, HER2/neu, Ki-67) were evaluated using odds ratios, relative risk estimates, χ^2 test, and Fisher's exact test. The IVS2+1G>A variant was significantly associated with hormone receptor–positive tumors, predominantly luminal subtypes, and was more frequently observed in postmenopausal patients. In contrast, the Ile157Thr polymorphism showed a wider age distribution and was linked to a heterogeneous molecular profile, including highly proliferative and triple-negative breast cancer subtypes. Distinct patterns of hormone receptor expression and Ki-67 levels suggested variant-specific biological behavior. These findings demonstrate that CHEK2 polymorphisms differentially influence breast cancer risk and phenotype in a menopause-dependent manner. The results highlight the importance of population-specific genetic profiling and support the potential utility of CHEK2 variants in personalized risk stratification for breast cancer in Uzbek women.

Keywords: CHEK2 gene; IVS2+1G>A polymorphism; Ile157Thr polymorphism; breast cancer; DNA damage response; genetic susceptibility; Uzbek population.

Introduction

It is well established that maternal health is a critical determinant of subsequent generations' health and economic well-being through intergenerational transmission mechanisms (Onarheim et al., 2016). Breast cancer (BC) remains one of the most prevalent and pressing oncological diseases affecting women worldwide (Kiani et al., 2025). According to data from the World Health Organization (WHO) and the Global Cancer Observatory (GLOBOCAN), more than 1.5 million new cases of breast cancer and associated deaths have been reported annually in recent years, and these figures are expected to rise in future (Akbar et al., 2022; Boonen, Vreeswijk, et al., 2022; Boonen, Wiegant, et al., 2023). The development of breast cancer is influenced by multiple factors, and its aetiology is characterised by the complex interplay between genetic susceptibility and environmental factors (Zhao et al., 2021). Recent studies suggest that moderate-penetrance genes, as well as high-penetrance genes such as BRCA1/2, TP53 and PALB2, play a significant role in breast cancer susceptibility (Baynes et al., 2007; Hauke et al., 2018; Blanter et al., 2020; Tahir et al., 2020; Tung et al., 2020; Darbeheshti et al., 2022), In addition, the role of moderate-penetrance genes such as CHEK2 and ATM in modulating breast cancer risk has been increasingly recognised (Acevedo et al., 2018; Ansari et al., 2019; CHEK2 Gene—GeneCards | CHK2 Protein | CHK2 Antibody. www.genecards.org/cgi-bin/carddisp.pl?gene=CHEK2). Mutations in these genes have been associated with a 2–5 fold increase in disease risk (Cybulski et al., 2004; Staples et al., 2017; Li et al., 2019). Table 1 summarises the key genes involved in hereditary predisposition to breast cancer, along with their biological functions and clinical relevance.

The CHEK2 gene (checkpoint kinase 2) is one of the key regulators involved in the cellular response to DNA damage. When DNA is

damaged, the ATM kinase phosphorylates the CHK2 protein encoded by the tumour suppressor CHEK2 gene at the Thr68 residue (threonine-68), inducing CHK2 dimerisation and activating autophosphorylation at the Ser516 and Thr387 residues. This results in the full functional engagement of the CHK2 kinase domain and enables the phosphorylation of critical downstream substrates involved in cell cycle control and apoptosis. These include TP53, BAX, CDKN1A/p21, CDC25A/CDC25C, BRCA1 and E2F1 (Nevanlinna & Bartek, 2006; Apostolou et al., 2018; Delimitsou et al., 2019; Li et al., 2020; Stolarova et al., 2020).

Table 1
Hereditary breast cancer susceptibility genes and their clinical significance

Gene	Function	Clinical association
	High-penetrance genes	
BRCA1	DNA repair	Triple-negative breast cancer with high hereditary predisposition (Agaoglu et al., 2022).
BRCA2	DNA repair	ER-positive subtype, bilateral breast cancer (Angeli et al., 2020).
TP53	Apoptosis and cell cycle regulation	Li–Fraumeni syndrome with early-onset clinical manifestations (McDonagh et al., 2021).
PALB2	BRCA2 as a co-factor in DNA repair	A risk level comparable to that of BRCA2 (Tischkowitz et al., 2021).
PTEN	Regulation of the *PI3K/AKT* signaling pathway	Cowden syndrome characterized by multiple tumors (Angeli et al., 2020).
	Moderate-penetrance genes	
CHEK2	*TP53* activation and cell cycle regulation	ER-positive subtype, contralateral breast cancer (Wei et al., 2022).
ATM	*CHEK2* activation in response to DNA damage	The risk is predominantly increased in HER2-positive cases (Chen et al., 2020).
RAD51C / RAD51D	*BRCA*-mediated DNA repair	Primarily associated with breast and ovarian cancer. (Apostolou & Papasotiriou, 2017).
BARD1	A BRCA1 partner in the DNA repair complex	Associated with an increased risk of ER subtypes (Hawsawi et al., 2022).

Note: Genes associated with hereditary breast cancer risk exhibit significant variations in penetrance, functional roles, and clinical significance. The table above highlights high- and moderate-penetrance genes (BRCA1, BRCA2, TP53, PALB2 and PTEN) that markedly increase the risk of developing breast cancer and are predominantly associated with familial forms of the disease. In contrast, moderate-penetrance genes (CHEK2, ATM, RAD51C, RAD51D and BARD1) confer a moderate yet clinically significant increase in tumour development risk. Together, these genes contribute to the early onset of disease and are primarily linked to the development of distinct, hormone-related breast cancer subtypes.

Disruptions to the function of the CHEK2 gene lead to the dysregulation of this signalling pathway. This results in impaired cell cycle control and insufficient DNA repair. Ultimately, this leads to the uncontrolled proliferation of malignant cells (Wu J. et al., 2019; Złowocka-Perłowska et al., 2019; Yu et al., 2021). Additionally, CHEK2 coordinates the DNA damage response signalling pathways involving DNA repair genes, such as XRCC1 and RAD51, thereby contributing to the restoration of damaged DNA. When DNA damage cannot be adequately repaired, CHEK2 promotes the activation of apoptotic pathways to ensure the elimination of damaged cells, thereby playing a critical role in preventing tumour cell development (Wu X. et al., 2001; Zeng et al., 2021; Zhang et al., 2021).

The CHEK2 IVS2+1G>A polymorphism is a splice-site mutation that occurs at the +1 position in intron 2, disrupting normal pre-mRNA splicing. This can lead to aberrant exon 2–3 junctions or complete skipping of exon 2, resulting in a frameshift and the generation of a premature stop codon. Consequently, instead of the full-length 543-amino acid protein, a truncated CHK2 protein consisting of 154 amino acids is produced. This truncated protein lacks both the FHA and kinase domains, undergoes rapid degradation due to misfolding or nonsense-mediated mRNA decay (NMD) and ultimately results in the loss of functional CHK2 activity (Cybulski et al., 2004; Nevanlinna & Bartek, 2006; Hu et al., 2012; Han et al., 2013; Mandelker et al., 2019;).

The CHEK2 Ile157Thr (c.470T>C, rs17879961) polymorphism, located in exon 3, is characterised by the substitution of isoleucine with threonine within the FHA domain (Anoushirvani et al., 2019; Wagener et al., 2023). This amino acid substitution reduces the interaction of the CHK2 protein with phosphorylated substrates, including CDC25 and BRCA1, thereby decreasing signal transduction efficiency. Consequently, while CHK2 retains the capacity to dimerise and undergo autophosphorylation, its ability to regulate the cell cycle via p53- and CDC25-mediated pathways is impaired (Liu et al., 2012). The Ile157Thr variant limits CDC25A degradation, enabling DNA replication to continue in the presence of DNA damage and promoting genomic instability and tumour cell proliferation. Previous studies have associated this polymorphism with breast cancer, as well as with colorectal, thyroid, renal and other malignancies. Overall, the CHEK2 Ile157Thr variant contributes to the attenuation of tumour suppressor mechanisms, thereby facilitating disease progression and an unfavourable prognosis (VCV000005591.103 – ClinVar, NCBI, 2024). Furthermore, studies conducted in Polish populations have demonstrated an association between CHEK2 IVS2+1G>A variants and an increased risk of developing breast cancer (Cybulski et al., 2004; Bell et al., 2007; Topaktaş et al., 2012; Weidner et al., 2020; Bono et al., 2021). Polymorphic variants of the CHEK2 gene, including IVS2+1G>A and Ile157Thr, have been extensively investigated in European and North American populations. Their associations with clinical phenotypes, hormone receptor status and disease prognosis are well documented (Han et al., 2013; Mandelker et al., 2019; Hu et al., 2021). However, data on these CHEK2 polymorphisms is limited in Central Asian populations, including the Uzbek population. This highlights the need for population-specific molecular epidemiological studies to identify regional genetic characteristics and improve genetic risk assessment at an individual level.

This study evaluated the distribution frequencies of the CHEK2 tumour suppressor gene polymorphisms IVS2+1G>A and Ile157Thr in the Uzbek population, alongside their associations with the clinical, pathological and immunohistochemical characteristics of patients with breast cancer. Such research could help identify region-specific genetic risk factors and provide deeper insight into the molecular mechanisms underlying breast cancer development.

Materials and methods

This study was conducted using a case–control design. A total of 200 patients diagnosed with breast cancer through mammographic and histopathological examinations were recruited from the Department of Mammology at the Republican Specialised Scientific and Practical Medical Centre of Oncology and Radiology of the Republic of Uzbekistan, as well as its Tashkent City Branch. The control group consisted of 100 Uzbek women who were considered healthy and had no clinical or instrumental evidence of breast cancer.

The clinical data of the patients, including their demographic characteristics, disease stage, biochemical parameters and immunohistochemical (IHC) findings, were collected from their medical records, including both outpatient and inpatient charts.

Three millilitres of peripheral venous blood were collected from all patients and control participants, and stored in tubes containing EDTA.

Genomic DNA was extracted from the blood samples using the AmpliPrime Ribo-Prep Kit (Next Bio, LLC, Russia), following the manufacturer's instructions. The concentration and purity of the DNA were then assessed using a NanoDrop 2000 spectrophotometer (Thermo Fisher Scientific, USA).

The IVS2+1G>A and Ile157Thr polymorphisms of the CHEK2 gene were determined using genetic test kits provided by Litekh (Russia). Amplification of the IVS2+1G>A polymorphism was per-

formed using conventional polymerase chain reaction (PCR) with a Corbett Research Gradient Palm Cycler CG1-96 (Australia). The Ile157Thr polymorphism was analysed using real-time PCR (RT-PCR) on a Rotor-Gene Q system (QIAGEN, Hilden, Germany).

All molecular genetic analyses were conducted at the Department of Molecular Medicine and Cell Technologies of the Republican Specialized Scientific and Practical Medical Centre of Haematology.

Statistical analyses were performed using R software (version 4.3.2). Differences between groups were evaluated using Pearson's chi-squared test, with the level of statistical significance set at $\alpha = 0.05$. Where expected cell counts were less than five, Fisher's exact test was used to calculate p-values (Waks & Winer, 2019).

Results

The frequencies of the CHEK2 IVS2+1G>A and Ile157Thr mutations were determined in the case and control groups (n = 300 in total). Among the 200 patients in the case group, six patients (3%) were identified as monoallelic carriers (heterozygous genotype, G/A) of the IVS2+1G>A mutation, while eight patients (4%) were identified as monoallelic carriers (heterozygous genotype, C/T) of the Ile157Thr mutation. In the control group (n = 100), the frequencies of the two mutations were identical, with one monoallelic carrier identified for each. No biallelic mutation carriers were observed among patients in the case group, and none of the patients' harbored mutations in both polymorphisms simultaneously (Fig. 1).

These results were used to analyse patients carrying the IVS2+1G>A and Ile157Thr mutations according to their age, tumour localization, disease subtype and stage, and immunohistochemical characteristics. These patients were then compared with the overall patient cohort (Table 2).

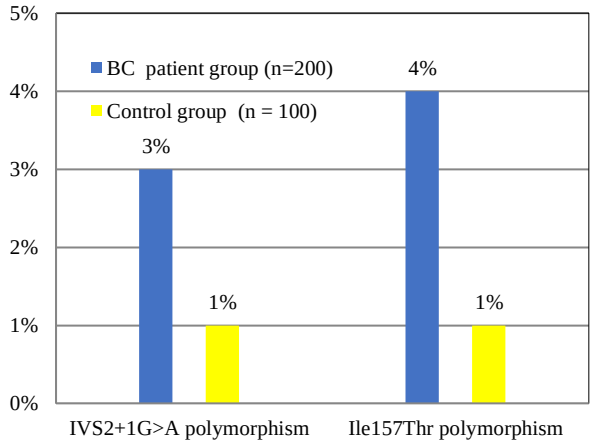

Fig. 1. Frequency of the CHEK2 IVS2+1G>A and Ile157Thr polymorphisms in breast cancer patients and the control group

Table 2
Major clinicopathological characteristics of breast cancer patients according to the investigated CHEK2 gene mutations

	Indicator	Overall group of patients with breast cancer (n = 200)	Group of patients carrying the CHEK2 IVS2+1G>A mutation		Group of patients carrying the CHEK2 Ile157Thr mutation	
Age of patients	<40	19 (9.5%)	–	OR = 1.06 95%; CI: 0.19–5.91; RR = 1.02 95%; CI: 0.57–1.81; $\chi^2 = 0.0037$; P = 1.000	1 (12.5%)	OR = 1.61 95%; CI: 0.32–8.19; RR = 1.15 95%; CI: 0.76–1.74; $\chi^2 = 0.3328$; P = 0.717
	40-60	131 (65.5%)	4 (66.7%)		6 (75.0%)	
	>60	50 (25.0%)	2 (33.3%)		1 (12.5%)	
Tumor location	Bilateral breast	2 (1.0%)	–	OR = 1.00 95%; CI: 0.20–5.08; RR = 1.00 95%; CI: 0.44–2.25; P = 1.000	–	OR = 1.00 95%; CI: 0.24–4.11; RR = 1.00 95%; CI: 0.49–2.03; P = 1.000
	Right breast	100 (59.0%)	3 (50.0%)		4 (50.0%)	
	Left breast	98 (49.0%)	3 (50.0%)		4 (50.0%)	
Breast cancer subtype (classification)	Luminal A	41 (20.3%)	2 (33.3%)	OR = 1.15 95%; CI: 0.21–6.46; RR = 1.05 95%; CI: 0.59–1.87; $\chi^2 = 0.0268$; P = 1.000	3 (37.5%)	OR = 1.76 95%; CI: 0.35–8.96; RR = 1.19 95%; CI: 0.79–1.80; $\chi^2 = 0.4755$; P = 0.713
	Luminal B	86 (42.9%)	2 (33.3%)		3 (37.5%)	
	HER2-enriched	43 (21.5%)	1 (16.7%)		–	
	TNBS (Triple-negative)	30 (15.2%)	1 (16.7%)		2 (25.0%)	
Disease stage	I	7 (3.6%)	1 (16.7%)	OR = 7.04 95%; CI: 0.39–126.85; RR = 1.54 95%; CI: 1.39–1.71; $\chi^2 = 3.1865$; P = 0.097	–	OR = 1.57 95%; CI: 0.31–8.00; RR = 1.14 95%; CI: 0.76–1.73; $\chi^2 = 0.3008$; P = 0.719
	II	125 (62.3%)	5 (83.3%)		6 (75.0%)	
	III	60 (29.9%)	–		2 (25.0%)	
	IV	8 (4.2%)	–		–	

Note: data are presented as absolute numbers (n) and percentages (%); percentages were calculated relative to the total number of patients in each group; patients carrying the IVS2+1G>A and Ile157Thr variants are monoallelic (heterozygous) mutation carriers only; due to small cell counts in several categories, statistical comparisons were performed using Fisher's exact test.

As shown in Table 2, most of the 200 breast cancer patients enrolled in the study were aged 40–60 years (65.5%, n = 131). This age group predominantly exhibits hormone receptor-dependent luminal molecular subtypes. Patients younger than 40 years old constituted 9.5% of the cohort. Breast cancer in this age group is known to be more aggressive and is more frequently associated with hereditary forms linked to mutations in genes such as BRCA1/2, CHEK2 and TP53. Patients over 60 years old represented 25% of the total cohort. This group is typically characterised by tumours that develop during the postmenopausal period and progress relatively slowly (Tian et al., 2018). In terms of tumour laterality, breast cancer predominantly developed unilaterally, which supports the well-established tendency for tumour occurrence in a single mammary gland (Willoughby et al., 2019; Yu et al., 2021; Zografos et al., 2021; Panegyres, 2024). Molecular subtype analysis revealed that 20.3% of patients in the main group were classified as luminal A, while 42.9% were classified as luminal B. These two subtypes together constituted the largest proportion of cases. HER2/neu-positive tumours accounted for 21.5% of cases, while triple-negative breast cancer (TNBC) was identified in 15.2% of patients. The distribution of disease stages indicated that 3.6% of patients were diagnosed at stage I, 62.3% at stage II, 29.9% at stage III and 4.2% at stage IV.

Among the six patients carrying the monoallelic IVS2+1G>A variant of the CHEK2 gene, mutation carriers were predominantly observed in the 40–60 age group (n = 4) and in patients over 60 (n = 2), with no carriers identified among those under 40. Statistical comparison revealed no significant increase in risk associated with the mutation across age groups (OR = 1.06; RR = 1.02; $\chi^2 = 0.0037$; P = 1.000). With respect to tumour laterality, IVS2+1G>A carriers demonstrated a symmetrical distribution between the right and left breasts (3:3), indicating no preferential association with tumour localisation (OR = 1.00; P = 1.000). Molecular subtype analysis showed that carriers of this variant were represented across luminal A, luminal B, HER2/neu-positive and triple-negative breast cancer (TNBC) subtypes, accounting for 33.3%, 33.3%, 16.7% and 16.7% of cases, respectively. Interestingly, all monoallelic IVS2+1G>A carriers were diagnosed at early clinical stages (I–II; 6/6), suggesting a tendency towards earlier-stage disease presentation. This was supported by a borderline statistical trend (OR = 7.04; $\chi^2 = 3.19$; P = 0.097).

Of the eight patients carrying the CHEK2 Ile157Thr missense variant, the majority (75%, n = 6) were in the 40–60 age group. Patients younger than 40 and older than 60 each accounted for 12.5% of cases. The presence of the Ile157Thr variant in all age categories suggests that the associated disease risk may manifest across a broad

age spectrum. Comparative analysis across age groups yielded an odds ratio (OR) of 1.61, a relative risk (RR) of 1.15, a chi-squared statistic (χ^2) of 0.33, and a p-value of 0.717, reflecting a heterogeneous age-related distribution pattern rather than a strict age-dependent effect.

In terms of tumour localisation, carriers of the monoallelic Ile157Thr variant exhibited a symmetrical distribution between the right and left breasts (4:4), suggesting that this mutation occurs independently of anatomical tumour localisation. Molecular subtyping revealed a predominance of luminal A and luminal B subtypes (37.5% each), while triple-negative breast cancer accounted for 25% of cases, suggesting an association between the Ile157Thr variant and less favourable clinical phenotypes.

Analysis of disease stage revealed a predominance of stage II and III tumours (6:2), indicating an intermediate to moderately aggressive clinical spectrum among Ile157Thr variant carriers. Statistical evaluation yielded an odds ratio (OR) of 1.57, a relative risk (RR) of 1.14, a chi-squared statistic (χ^2) of 0.30, and a p-value of 0.719, characterising the stage distribution pattern observed in this subgroup.

It is well established that biomarkers play a crucial role in the early detection, monitoring, and prognostication of disease progression by providing valuable insights into the biological mechanisms underlying pathological processes (Akhtam et al., 2025). Immunohistochemical analysis also revealed distinct expression profiles of hormonal and proliferative markers in patients with monoallelic CHEK2 IVS2+1G>A and Ile157Thr mutations, as summarised in Table 3.

Table 3

Immunohistochemical (IHC) characteristics of breast cancer associated with tumor suppressor CHEK2 gene mutations

Immunohistochemical markers		Breast cancer patient group (n = 200)	*CHEK2* IVS2+1G>A–positive patients (study group) (n = 6)		*CHEK2* Ile157Thr positive patients (study group) (n = 8)	
Estrogen Receptor	+	124 (62.0%)	4 (66.7%)	OR = 1.23 95%; Cl: 0.22–6.90; RR = 1.08 95%; Cl: 0.61–1.92; χ^2 = 0.0036; P = 1.000	6 (75.0%)	OR = 1.84 95%; Cl: 0.36–9.36; RR = 1.21 95%; Cl: 0.80–1.83; χ^2 = 0.56; P = 0.71
	-	76 (38.0%)	2 (33.3%)		2 (25.0%)	
Progesterone Receptor	+	115 (57.5%0	5 (83.3%	OR = 3.82 95%; Cl: 0.44–33.30; RR = 1.47 95%; Cl: 1.01–2.15; χ^2 = 0.78; P = 0.379	5 (62.5%)	OR = 1.24 95%; Cl: 0.29–5.35; RR = 1.09 95%; Cl: 0.63–1.89; χ^2 = 0.09; P = 1.000
	-	85 (42.5%)	1 (16.7%)		3 (37.5%)	
Human Epidermal Growth Factor Receptor 2	+	56 (28.0%)	2 (33.3%)	OR = 1.30 95%; Cl: 0.23–7.28; RR = 1.20 95%; Cl: 0.38–3.80; χ^2 = 0.0029; P = 1.000	1 (12.5%)	OR = 0.37 95%; Cl: 0.04–3.04; RR = 0.44 95%; Cl: 0.07–2.82; χ^2 = 0.33; P =0.450
	-	144 (72.0%)	4 (66.7%)		7 (87.5%)	
Ki-67 Proliferation Index	+	167 (83.5%)	5 (83.3%)	OR = 0.99 95%; Cl: 0.11–8.74; RR = 1.00 95%; Cl: 0.69–1.44; χ^2 = 0.0001; P = 1.000	6 (75.0%)	OR = 0.58 95%; Cl: 0.11–3.00; RR = 0.89 95%; Cl: 0.60; χ^2 = 0.44; P = 0.51
	-	33 (16.5%)	1 (16.7%)		2 (25.0%)	

Note: Distribution of ER, PR, HER2 and Ki-67 expression in the main breast cancer cohort (n = 200), and in patients from the main group carrying the CHEK2 IVS2+1G>A variant (n = 6) or the Ile157Thr variant (n = 8). '+' indicates positive expression and '–' indicates negative expression. Ki-67 values >15% were classified as positive, while values <15% were classified as negative.

ER receptor positivity was slightly higher among carriers of the G/A genotype of the IVS2+1G>A polymorphism (66.7%) than among patients carrying the G/G genotype (61.9%). These results are reflected in an odds ratio (OR) of 1.23 (95% confidence interval (CI): 0.22–6.90), a relative risk (RR) of 1.08 (95% CI: 0.61–1.92) and a chi-squared (χ^2) value of 0.0036 (P = 1.000). These findings suggest a tendency towards an ER-positive phenotype among G/A genotype carriers. For the Ile157Thr polymorphism, ER-positive expression was observed in 75% of patients carrying the C/T genotype. This association was characterised by an odds ratio (OR) of 1.84 (95% confidence interval (CI): 0.36–9.36), a relative risk (RR) of 1.21 (95% CI: 0.80–1.83) and a chi-squared (χ^2) value of 0.56 (P = 0.71), suggesting a higher prevalence of ER positivity among Ile157Thr variant carriers.

Progesterone receptor (PR) positivity was more prevalent among carriers of the G/A genotype of the IVS2+1G>A polymorphism (83.3%). This distribution was characterised by an odds ratio (OR) of 3.82 (95% confidence interval (CI): 0.44–33.30), a relative risk (RR) of 1.47 (95% CI: 1.01–2.15) and a chi-squared (χ^2) value of 0.78 (P = 0.379), reflecting a tendency towards a PR-positive phenotype in this genotype group. For the Ile157Thr variant, PR expression was characterised by an OR of 1.24 (95% CI: 0.29–5.35), an RR of 1.09 (95% CI: 0.63–1.89) and a chi-squared value of 0.09 (P = 1.000).

HER2/neu expression among IVS2+1G>A G/A genotype carriers was 33.3%, represented by an OR of 1.30 (95% CI: 0.23–7.28), an RR of 1.20 (95% CI: 0.38–3.80) and a χ^2 value of 0.0029 (P = 1.000). By contrast, the Ile157Thr polymorphism showed lower HER2/neu positivity: OR = 0.37 (95% CI: 0.04–3.04), RR = 0.44 (95% CI: 0.07–2.82) and χ^2 = 0.33 (P = 0.45). This indicates genotype-dependent variation in marker distribution.

The Ki-67 proliferation index among IVS2+1G>A variant carriers was comparable to that of the overall patient cohort (83.3–83.5%), defined by OR = 0.99 (95% CI: 0.11–8.74), RR = 1.00 (95% CI: 0.69–1.44) and χ^2 = 0.0001 (P = 1.000). For the Ile157Thr polymorphism, Ki-67 positivity reached 85%, with an odds ratio (OR) of 0.58 (95% confidence interval (CI): 0.11–3.00), relative risk (RR) of 0.89, and chi-squared (χ^2) value of 0.44 (P = 0.51), positioning this variant within a distinct proliferative activity spectrum. Overall, these findings suggest that the IVS2+1G>A polymorphism is more closely associated with hormonal receptor-related phenotypes, particularly PR and ER, whereas the Ile157Thr variant exhibits differential phenotypic distributions across HER2/neu and Ki-67 markers. Together, these patterns support the role of CHEK2 variants as modulators of molecular phenotype heterogeneity in breast cancer.

This study analysed the distribution of allelic and genotypic variants of the CHEK2 IVS2+1G>A and Ile157Thr polymorphisms in women with breast cancer, taking menopausal status into consideration. Patients in the case group were stratified into two biologically relevant subgroups: A1: postmenopausal women (aged ≥50 years or with ≥12 months since cessation of menstruation); and A2: premenopausal women (aged <50 years). This enabled the assessment of potential interactions between menopause-related hormonal changes and genetic risk factors associated with breast cancer susceptibility.

For the IVS2+1G>A polymorphism, a comparative analysis of the A1 subgroup and the control group revealed that the G major allele was associated with lower odds and relative risk values (OR = 0.27; RR = 0.28). This suggests a protective effect of the G allele in postmenopausal women. Similarly, the G/G genotype showed low association with disease risk (OR = 0.37; RR = 0.97), suggesting a more stable phenotypic background associated with this genotype.

By contrast, the A minor allele and the G/A genotype were characterised by substantially higher risk estimates in the case group, particularly when the A1 (postmenopausal) subgroup was compared with the control group. Specifically, the G/A genotype showed markedly higher odds and relative risk values (OR = 4.64; RR = 4.93), suggesting a stronger link between the IVS2+1G>A polymorphism and breast cancer risk in postmenopausal women. However, in comparisons between the A2 (premenopausal) subgroup and the control group, the corresponding risk estimates were lower, suggesting that the genetic association of this polymorphism is weaker during the premenopausal period. Direct comparison between the A1 and A2 subgroups further supported the predominance of A-allele- and G/A-genotype-associated risk in postmenopausal women.

Analysis of the Ile157Thr polymorphism likewise revealed menopause-dependent differential patterns. The C major allele and the C/C genotype were consistently associated with lower odds ratios (OR) and relative risk (RR) values across all comparative groups (OR = 0.26–0.27; RR = 0.27–0.96), reflecting a relatively stable molecular background linked to this allelic configuration. Conversely, the T minor allele and the C/T genotype were characterised by increased risk estimates in both the A1 and A2 subgroups compared to the control group. Notably, the comparison between the A2 subgroup and the control group revealed particularly high-risk values for the T allele (OR = 4.78; RR = 4.69), suggesting that the Ile157Thr polymorphism predominantly acts as a risk-enhancing factor in the premenopausal period. Overall, the findings of this study suggest that menopausal status is a significant biological factor that influences the relationship between the CHEK2 IVS2+1G>A and Ile157Thr polymorphisms and breast cancer risk. The predominance of the IVS2+1G>A-associated risk factor in postmenopausal women, alongside the stronger association of the Ile157Thr polymorphism during the premenopausal period, highlights the complex interactions between the hormonal environment and genetic susceptibility. These patterns suggest that CHEK2 genetic variants have selective effects on breast cancer development that depend on age and menopause, reflecting the fact that DNA damage response pathways may be modulated differently in different biological contexts (Table 4).

Table 4

Differences in the distribution of CHEK2 IVS2+1G>A and Ile157Thr mutations among the A1, A2, and control groups

Polymorphism	Allele and genotype	A1 and control groups		A2 and control groups		A1 and A2 groups	
		OR	RR	OR	RR	OR	RR
IVS2+1G>A	G allele	0.27	0.28	0.80	0.80	0.45	0.99
		n* = 267		n* = 127		n* = 199	
	A allele	0.65	3.56	1.57	1.56	2.23	2.18
		n* = 5		n* = 1		n* = 1	
	G/G genotype	0.37	0.97	0.64	0.99	0.48	0.98
		n = 131		n = 63		n = 99	
	G/A genotype	4.64	4.93	1.57	1.56	2.34	2.27
		n = 5		n = 1		n = 1	
Ile157Thr	C allele	0.27	0.27	0.21	0.21	0.78	0.99
		n* = 267		n* = 125		n* = 199	
	T allele	3.73	3.68	4.78	4.69	1.28	1.28
		n* = 5		n* = 3		n* = 1	
	C/C genotype	0.26	0.27	0.21	0.96	0.78	0.99
		n = 131		n = 61		n = 99	
	C/T genotype	3.78	3.68	4.87	4.69	1.29	1.28
		n = 5		n = 3		n = 1	

Note: n* - number of alleles, n- number of genotypes.

Discussion

This study's results demonstrate a close relationship between the clinical and molecular characteristics of breast cancer, patient age, menopausal status and functionally relevant CHEK2 gene polymorphisms. The predominance of patients within the 40–60 age range may be attributed to increased hormonal signalling pathway activity during this period, consistent with the higher prevalence of luminal molecular subtypes. This finding is consistent with previously published epidemiological data and highlights the interaction between the oestrogen-progesterone hormonal environment and genetic predisposition.

The CHEK2 IVS2+1G>A polymorphism exhibited a clinically relevant pattern, predominantly occurring in middle-aged and older patients, particularly during the postmenopausal period, showing a closer association with hormone receptor-positive luminal phenotypes. Through its impact on pre-mRNA splicing, this variant may modulate CHK2 protein functionality, thereby influencing the reprogramming of DNA damage response pathways under conditions of altered hormonal signalling. The tendency towards earlier clinical-stage presentation suggests that IVS2+1G>A is associated with less aggressive yet clinically significant tumour phenotypes, highlighting its potential relevance in breast cancer risk stratification.

The Ile157Thr missense polymorphism exhibited a broader age distribution and was characterised by heterogeneous molecular clinical phenotypes. Structural and functional alterations within the FHA domain may modulate CHEK2 interactions with phosphorylated substrates, thereby influencing cell-cycle regulation and proliferative control. In addition to luminal subtypes, the presence of triple-negative breast cancer (TNBC) among Ile157Thr carriers indicates a link with more aggressive tumour characteristics. Immunohistochemical profiling further highlighted distinct functional patterns between the two CHEK2 variants. The IVS2+1G>A polymorphism showed closer functional alignment with oestrogen and progesterone receptor expression in particular, whereas the Ile157Thr variant was associated with differential distributions of HER2/neu and Ki-67, reflecting variability in proliferative signalling. These findings suggest that CHEK2 variants have different effects on hormonal signalling pathways and proliferation-related mechanisms.

Stratified analyses incorporating menopausal status revealed that the IVS2+1G>A polymorphism showed stronger associations with breast cancer risk in postmenopausal women, while the Ile157Thr variant demonstrated a more pronounced association during the premenopausal period. Taken together, these observations emphasise the stage-dependent and context-specific interplay between the hormonal environment and CHEK2 genetic variation, which contributes to the heterogeneity of breast cancer risk and molecular phenotype. Overall, the present study demonstrates that the IVS2+1G>A and Ile157Thr polymorphisms of the CHEK2 gene are important determinants that modulate the molecular phenotype and clinical spectrum of breast cancer. The observed associations emphasise the significance of CHEK2 genetic variation in shaping hormone-related, proliferative and stage-specific tumour characteristics. Notably, these findings provide a scientific basis for population-specific risk stratification in Central Asia, particularly within the Uzbek population, considering age- and menopause-related biological contexts. Incorporating CHEK2 variants into genetically informed screening and prevention strategies could enhance the accuracy of individualised risk assessment and facilitate earlier detection. Further validation in larger cohorts and functional studies is essential to refine the clinical relevance of these associations and clarify the mechanistic pathways through which CHEK2 variants contribute to breast cancer development and progression.

Conclusion

This study demonstrates that the CHEK2 IVS2+1G>A and Ile157Thr polymorphisms contribute differently to the molecular and clinical heterogeneity of breast cancer in the Uzbek population. The IVS2+1G>A variant is more closely associated with hormone receptor-positive phenotypes, particularly ER- and PR-positive tumours, and is associated with a higher risk in postmenopausal women, suggesting an interaction with the hormonal environment that depends on the context. In contrast, the Ile157Thr missense variant is observed across a broader age range and is characterised by a more heterogeneous molecular profile, including an increased representation of proliferative and triple-negative phenotypes. This indicates its potential involvement in cell cycle dysregulation and tumour aggressiveness. Stratified analysis by menopausal status reveals that menopause is a significant biological modifier of CHEK2-related cancer risk. Taken together, these findings support the role of CHEK2 genetic variants as modulators of breast cancer phenotype and risk in a population-specific manner, providing a rationale for incorporating age and menopausal status into genetic risk assessment and personalised screening strategies.

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