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TP53 GENE POLYMORPHISM AND BREAST CANCER RISK IN RADIATION-EXPOSED KAZAKH WOMEN

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Abstract

Background. TP53 rs1042522 (Arg72Pro) is a functionally significant polymorphism that alters the apoptotic activity of the p53 protein and is potentially associated with cancer susceptibility. Its contribution to cancer risk in radiation-exposed populations remains insufficiently explored. This study aimed to analyze the frequency of this polymorphism in women with breast cancer residing near the former Semipalatinsk nuclear test site, considering both hereditary and environmental risk factors.

Materials and methods. A case-control study was conducted involving 250 Kazakh women aged 40 to 79 years. Participants were categorized into groups based on cancer diagnosis, family history, and radiation exposure. Genotyping of the TP53 rs1042522 polymorphism was performed using real-time PCR. Statistical analysis included calculation of odds ratios (OR) with 95% confidence intervals (CIs), with Bonferroni correction applied where necessary.

Results. The frequency of GC/CC genotypes was significantly higher among breast cancer patients with both a family history and documented radiation exposure (OR = 6.91; 95% CI: 1.89–25.21; p = 0.0020). A meaningful association was also observed in sporadic breast cancer cases – women with no known familial or radiation-related predisposition (OR = 4.30; 95% CI: 1.15–16.09; p = 0.0269). Genotype distribution in the control group was consistent with Hardy-Weinberg equilibrium, supporting the validity of sampling and genotyping procedures.

Conclusion. The findings of this study suggest that the TP53 rs1042522 polymorphism may contribute to increased susceptibility to breast cancer in women exposed to ionizing radiation. These results highlight the importance of an integrated approach to cancer risk assessment that includes both genetic and environmental factors, and emphasize the need for further investigation of TP53 as a potential biomarker in vulnerable populations.

Keywords: *TP53, Arg72Pro, breast cancer, Semipalatinsk, polymorphism, radiation exposure, Kazakhstan, gene-environment interaction.*

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Резюме

ПОЛИМОРФИЗМ ГЕНА *TP53* И РИСК РАКА МОЛОЧНОЙ ЖЕЛЕЗЫ У ЖЕНЩИН КАЗАХСКОЙ НАЦИОНАЛЬНОСТИ, ПОДВЕРГШИХСЯ РАДИАЦИОННОМУ ВОЗДЕЙСТВИЮ

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Введение. TP53 rs1042522 (Arg72Pro) – функционально значимый полиморфизм, изменяющий апоптотическую активность белка p53 и потенциально ассоциированный с онкологической предрасположенностью. Влияние данного варианта на риск развития рака в условиях хронического радиационного воздействия остается недостаточно изученным. Настоящее исследование направлено на анализ частоты данного полиморфизма у женщин с раком молочной железы, проживающих вблизи бывшего Семипалатинского испытательного полигона, с учетом семейного анамнеза и истории радиационного воздействия.

Материалы и методы. Исследование случай-контроль, включившее 250 женщин казахской национальности в возрасте от 40 до 79 лет. Участницы были разделены на группы в зависимости от диагноза, семейного анамнеза и

радиационного воздействия. Генотипирование *TP53* rs1042522 проводилось методом ПЦР в режиме реального времени. Статистический анализ включал расчет отношений шансов (OR) с 95% доверительными интервалами (CI) и поправку Бонферрони.

Результаты. Частота генотипов GC/CC была достоверно выше среди женщин с раком молочной железы, имеющих как семейную отягощенность, так и историю радиационного воздействия (OR = 6,91; 95% CI: 1,89–25,21; p = 0,0020). Существенная ассоциация также наблюдалась в группе спорадических случаев – у пациенток без наследственной и радиационной предрасположенности (OR = 4,30; 95% CI: 1,15–16,09; p = 0,0269). В контрольной группе распределение генотипов соответствовало равновесию Харди-Вайнберга, что подтверждает корректность выборки и генотипирования.

Выводы. Результаты исследования позволяют предположить участие полиморфизма *TP53* rs1042522 в повышении чувствительности к раку молочной железы у женщин, подвергшихся радиационному воздействию. Это подчеркивает актуальность комплексного подхода к оценке онкогенного риска, включающего как генетические, так и экологические параметры, а также необходимость дальнейшего изучения TP53 как потенциального биомаркера.

Ключевые слова: *TP53, Arg72Pro, рак молочной железы, Семипалатинск, полиморфизм, радиационное воздействие, Казахстан, взаимодействие гена и среды.*

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Түйіндеме

TP53 ГЕНІНІҢ ПОЛИМОРФИЗМІ ЖӘНЕ РАДИАЦИЯЛЫҚ ӘСЕРГЕ ҰШЫРАҒАН ҚАЗАҚ ӘЙЕЛДЕРІНДЕГІ СҮТ БЕЗІ ОБЫРЫНЫҢ ДАМУ ҚАУПІ

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Кіріспе. TP53 rs1042522 (Arg72Pro) – p53 ақуызының апоптоздық белсенділігіне әсер ететін функционалды маңызды полиморфизм және онкологиялық бейімділікпен ықтимал байланысты генетикалық маркер. Бұл варианттың радиациялық әсерге ұшыраған адамдарда қатерлі ісік қаупіне әсері жеткілікті зерттелмеген. Осы зерттеудің мақсаты – бұрынғы Семей ядролық полигонына жақын аймақтарда тұратын, сүт безі обыры бар әйелдер арасында осы полиморфизм жиілігін, сондай-ақ олардың отбасылық анамнезі мен радиациялық әсер тарихын ескере отырып талдау.

Материалдар мен әдістер. Бұл зерттеу 40-79 жас аралығындағы 250 қазақ ұлтының әйелдері арасында жүргізілген жағдай–бақылау типіндегі зерттеу болды. Қатысушылар сүт безі обыры диагнозы, отбасылық анамнез және радиациялық әсер деректері бойынша топтарға бөлінді. TP53 rs1042522 полиморфизмін генотиптеу нақты уақыттағы ПТР әдісімен жүргізілді. Статистикалық талдау 95% сенімділік интервалдары (CI) бар ықтималдық коэффициенттерін (OR) есептеуді қамтыды, қажет болған жағдайда Бонферрони түзетуі қолданылды.

Нәтижелер. GC/CC генотиптерінің жиілігі отбасылық анамнезі мен радиациялық әсері бар сүт безі обырымен ауырған әйелдер арасында едәуір жоғары болды (OR = 6.91; 95% CI: 1.89–25.21; p = 0.0020). Мұндай байланысты отбасылық және радиациялық тәуекел факторлары жоқ, спорадиялық сүт безі обыры жағдайларынан да байқауға болады (OR = 4.30; 95% CI: 1.15–16.09; p = 0.0269). Бақылау тобындағы генотиптердің таралуы Харди–Вайнберг тепе-теңдігіне сәйкес келді, бұл іріктеу мен генотиптеу сенімділігін көрсетеді.

Қорытынды. Бұл зерттеудің нәтижелері *TP53* rs1042522 полиморфизмінің радиациялық әсерге ұшыраған әйелдерде сүт безі обырына бейімділікті арттыруы мүмкін екенін көрсетеді. Бұл онкологиялық қауіп-қатерді бағалауда генетикалық және экологиялық факторларды біріктіретін кешенді тәсілдің маңыздылығын атап көрсетеді, сондай-ақ TP53 генін болашағы бар биомаркер ретінде әрі қарай зерттеу қажеттілігін көрсетеді.

Түйінді сөздер: *TP53, Arg72Pro, сүт безі обыры, Семей, полиморфизм, радиациялық әсер, Қазақстан, ген-орта әрекеттестігі.*

Дәйексөз үшін:

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Introduction

Breast cancer remains the most frequently diagnosed malignancy and one of the leading causes of cancer-related death among women globally. According to GLOBOCAN 2022, approximately 2.3 million new cases and 670,000 deaths were reported worldwide in that year [15]. The etiology of breast cancer is multifactorial, involving both inherited genetic predispositions and environmental exposures [18]. These disparities may reflect differences in screening practices, lifestyle factors, and genetic background.

The global variation in breast cancer incidence is illustrated in Figure 1, which presents age-standardized rates across selected countries. The highest incidence is observed in the United States and Germany, while rates remain comparatively lower in China and Kazakhstan.

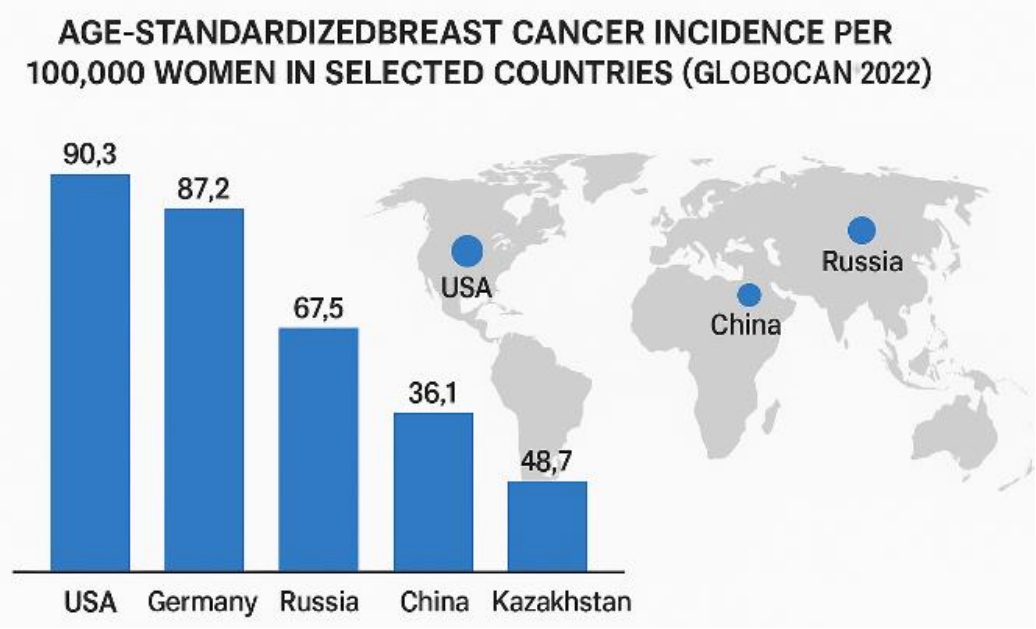

Figure 1. Global distribution of age-standardized breast cancer incidence (per 100,000 women).

In regions affected by long-term radioactive contamination, such as the Semipalatinsk Test Site in Kazakhstan, chronic exposure to ionizing radiation has raised major concerns regarding transgenerational health risks, including carcinogenesis [1,9]. Ionizing radiation is a well-established mutagen that induces DNA damage and genomic instability, which may synergize with inherited mutations to elevate cancer susceptibility [12].

Among the critical tumor suppressor genes involved in genome surveillance is TP53, which encodes the p53 protein. This protein plays a central role in regulating DNA repair, cell cycle arrest, and apoptosis in response to genotoxic stress [11]. A widely studied polymorphism of TP53, rs1042522 (Arg72Pro), results in an amino acid substitution that affects the apoptotic efficiency of the protein. This polymorphism has been associated with variable cancer risk, including breast cancer [17,19]. Although its role has been extensively evaluated in multiple populations, the prevalence and functional significance of this variant remain insufficiently investigated in radiation-exposed populations.

The aim of this study was to assess the frequency of the TP53 rs1042522 polymorphism in breast cancer patients with or without a family history of cancer and radiation exposure in the Semipalatinsk region. We hypothesized that women with both a familial predisposition and a history of radiation exposure would exhibit a significantly higher prevalence of this polymorphism compared to non-exposed healthy controls.

Materials and Methods

This cross-sectional case-control study included a total of 250 women of Kazakh nationality aged 40 to 79 years, recruited between 2015 and 2017 from Semey Oncology Center and local medical facilities in the East Kazakhstan region. All participants provided written informed consent. The study protocol was approved by the institutional ethics committee and adhered to the principles outlined in the Declaration of Helsinki.

Inclusion Criteria: women aged between 40 and 79 years; Kazakh ethnicity confirmed through official documentation (national ID and birth certificates of the participant and both parents); histologically confirmed diagnosis of breast cancer (for cases); no history of any malignancy (for controls); availability of reliable data on family cancer history and residential/radiation exposure history.

Exclusion Criteria: participants were excluded if they were of non-Kazakh ethnicity or had at least one parent of non-Kazakh origin, in order to minimize population stratification and genetic heterogeneity; had other malignancies apart from breast cancer; were older than 80 years (due to potential survivorship bias); had insufficient DNA quality for genotyping; had incomplete clinical or exposure data.

Participants were categorized into four analytical subgroups based on diagnosis and exposure history:

Group A – Women with breast cancer, family history of breast cancer, and documented radiation exposure (either direct or parental exposure due to residence near the Semipalatinsk Test Site).

Group B – Women with breast cancer and family history but without radiation exposure.

Group C – Women with breast cancer without family or radiation history.

Control Group – Healthy women without breast cancer, family history, or radiation exposure.

Age subgroups were created (≥60 years and <60 years) to distinguish between potentially directly irradiated individuals and descendants.

The demographic and clinical characteristics of each group are presented in Table 1.

Table 1.

Distribution of study participants by clinical and exposure characteristics.

Group	Subgroup	Description	N	% within group	Mean Age (± SD)
Group A (Breast cancer + family history + radiation exposure)	A1	Directly exposed women (≥60 years)	25	41.7%	66.2 ± 2.4
	A2	Descendants of exposed (<60 years)	35	58.3%	61.8 ± 2.6
Group B (Breast cancer + family history, no radiation)	B1	Age ≥60 years	30	46.2%	65.1 ± 2.5
	B2	Age <60 years	35	53.8%	62.3 ± 2.2
Group C (Breast cancer, no family history, no radiation)	C1	Age ≥60 years	35	53.8%	66.5 ± 2.3
	C2	Age <60 years	30	46.2%	63.0 ± 2.4
Control Group (No breast cancer, no family history, no radiation)	D1	Age ≥60 years	30	50.0%	69.3 ± 2.1
	D2	Age <60 years	30	50.0%	65.7 ± 2.7
Total	-	-	250	100%	-

Notes:
Subgrouping based on age (<60 and ≥60) was used to approximate directly irradiated women vs. descendants.
No statistically significant age differences were observed between the main groups ($p > 0.05$).
Mean ages calculated separately per subgroup to account for exposure history and age-related risk.

Sample Size and Power Calculation

A sample size of 250 participants (190 cases and 60 controls) was calculated based on a two-sided Fisher's exact test with a significance level of $\alpha = 0.05$ and power $(1–\beta) = 0.80$. Based on prior literature [1], an estimated difference in TP53 rs1042522 polymorphism frequency between exposed cases and unexposed controls of at least 20% was expected. The calculated power was sufficient to detect odds ratios >2.0 with confidence intervals of ±10%.

Genotyping Procedure

Peripheral blood samples (5 mL) were collected in EDTA-coated tubes. Genomic DNA was extracted using the "Standard-NC" kit (DNA-Technology, Moscow, Russia) according to the manufacturer's protocol. DNA quality and concentration were assessed using the NanoDrop 1000 spectrophotometer (Thermo Fisher Scientific, USA). Samples were stored at −20°C until analysis.

Genotyping of the TP53 rs1042522 polymorphism was performed using Real-Time PCR with TaqMan Genotyping Assays (Applied Biosystems) on a 7500 Fast Real-Time PCR System. Each reaction included 50 ng of genomic DNA. PCR cycling conditions were: 95°C for 10 minutes (initial denaturation), followed by 40 cycles of 95°C for 15 seconds and 60°C for 1 minute. All genotyping reactions were performed in duplicate to ensure reproducibility and accuracy.

Statistical Analysis

Allele and genotype frequencies were compared using Fisher's exact test. Associations were expressed as odds ratios (ORs) with 95% confidence intervals (CIs). A p-value <0.05 was considered statistically significant. Correction for multiple testing (Bonferroni method) was applied where appropriate. All statistical analyses were performed using SPSS Statistics v25.0 (IBM Corp, USA). HWE was assessed for the control group using the chi-square test.

Results

To assess the strength of association between the TP53 rs1042522 polymorphism and breast cancer risk, odds ratios (ORs) with 95% confidence intervals (CIs) were calculated for each case group in comparison to the control group.

Women with a positive family history and radiation exposure (Group A) demonstrated the highest risk of carrying the GC or CC genotype, with an OR of 6.91 (95% CI: 1.89–25.21; $p = 0.0020$). Group C (sporadic breast cancer) also showed a statistically significant association: OR = 4.30 (95% CI: 1.15–16.09; $p = 0.0269$). Group B (familial history only) demonstrated a non-significant trend (OR = 3.45; $p = 0.0788$).

Figure 2 illustrates the frequency of individuals carrying the GC or CC genotypes (combined) across all study groups, including 95% confidence intervals.

Hardy-Weinberg Equilibrium (HWE) analysis in the control group revealed allele frequencies of G = 91.7% and C = 8.3%. Observed genotype counts were GG = 51, GC = 8, and CC = 1; expected counts under HWE were GG = 50.4, GC = 9.2, and CC = 0.4. The chi-square test yielded $\chi^2 = 0.97$, $p = 0.324$, indicating no significant deviation from HWE.

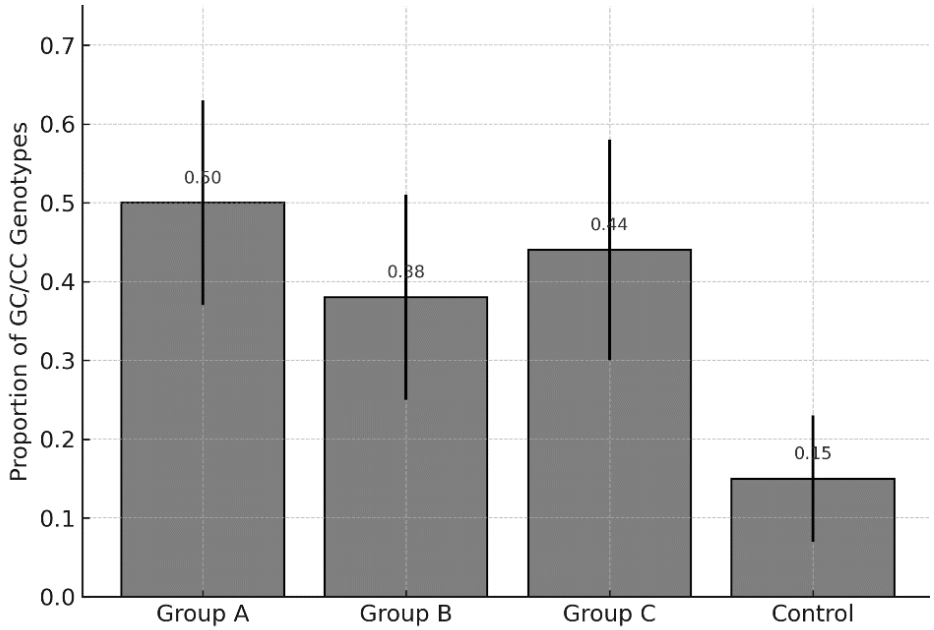

Figure 2. Frequency of TP53 rs1042522 GC/CC genotypes by group. Error bars indicate 95% confidence intervals.

Figure 3 shows the proportional distribution of genotypes (GG, GC, CC) in each group, highlighting structural differences in genotype composition.

Corresponding genotype frequencies in absolute values and percentages are summarized in Table 2.

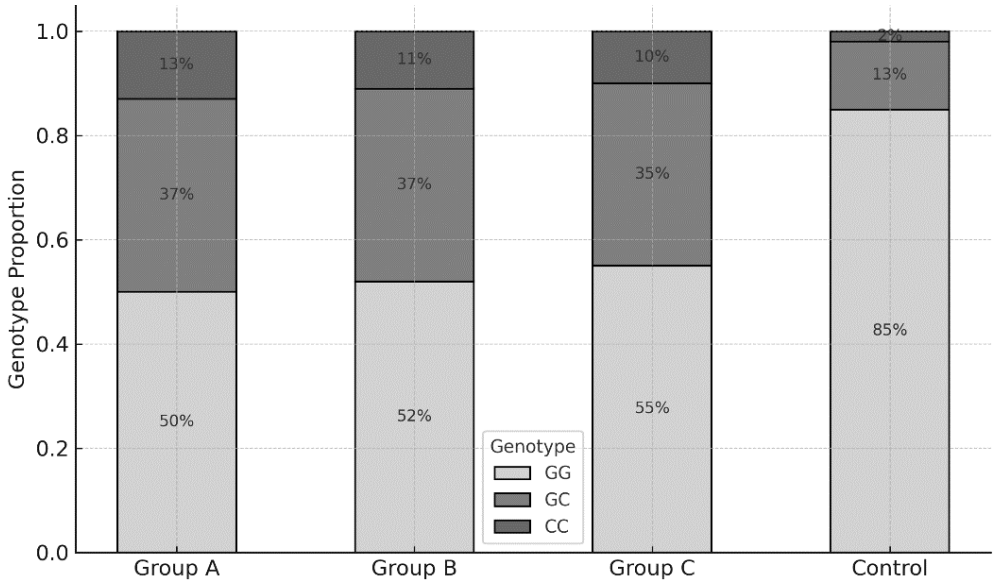

Figure 3 – Relative distribution of TP53 rs1042522 genotypes across study groups. Each bar represents 100% of participants in the group, subdivided by genotype.

Table 2

Distribution of TP53 rs1042522 (Arg72Pro) genotypes across study groups (n and %).

Group	GG (Arg/Arg)	GC (Arg/Pro)	CC (Pro/Pro)	Total
BC + FamHist + RadHist	30 (50.0%)	22 (36.7%)	8 (13.3%)	60
BC + FamHist	34 (52.3%)	24 (36.9%)	7 (10.8%)	65
BC only	36 (55.4%)	23 (35.4%)	6 (9.2%)	65
Healthy controls	51 (85.0%)	8 (13.3%)	1 (1.7%)	60

Taken together, the results demonstrate a significantly higher prevalence of the TP53 rs1042522 GC/CC genotypes among breast cancer patients with both familial and radiation exposure histories. The genotype distribution was consistent with Hardy-Weinberg Equilibrium in the control group, supporting the validity of the genetic data.

These findings suggest a potential gene-environment interaction contributing to breast cancer susceptibility in the Semipalatinsk-exposed population.

Discussion

This study provides new insights into the distribution of the TP53 rs1042522 (Arg72Pro) polymorphism among breast cancer patients residing in a historically radiation-exposed region. The findings suggest that individuals with both a family history of breast cancer and radiation exposure (Group A) exhibit the highest frequency of GC/CC genotypes, supporting the hypothesis of a gene–environment interaction in breast cancer susceptibility.

The Arg72Pro polymorphism affects the pro-apoptotic capacity of the p53 protein. The Pro variant has been reported to be less efficient in inducing apoptosis, potentially allowing survival of genetically damaged cells and contributing to tumor development [4]. Our observation that the GC/CC genotype was significantly more common among women with dual risk factors is consistent with the functional impact of this variant and the biological plausibility of interaction with radiation-induced DNA damage.

Several previous studies have identified the TP53 rs1042522 polymorphism as a low-penetrance genetic factor associated with breast cancer risk, particularly in East Asian and Slavic populations [7,20]. A meta-analysis by Zhang et al. and other regional reviews confirmed that the Pro allele may increase breast cancer risk modestly, especially under recessive and dominant models [3,7,20].

Our results support the relevance of this variant in Central Asian populations and extend observations made in South Asian [7], Middle Eastern [5], and Latin American [14] cohorts. For example, in a study conducted in Egypt, the GC/CC genotypes were significantly more frequent among breast cancer patients than controls, with an OR similar to that observed in our study [5]. Likewise, a Brazilian study reported higher prevalence of the Pro allele among young women with breast cancer [14]. These findings collectively suggest that while the absolute frequencies of genotypes may differ between populations, the risk association remains biologically consistent.

Ionizing radiation is a well-established carcinogen that induces DNA double-strand breaks and genomic instability, creating a permissive background for the emergence and clonal expansion of premalignant cells [16]. In individuals carrying the Pro variant of p53, impaired apoptosis may hinder the elimination of such damaged cells, increasing the likelihood of oncogenic transformation. The observed increase in GC/CC genotypes among exposed individuals and their descendants suggests that radiation may act not only as a direct mutagen but also as a modifier of genotype penetrance. These findings align with studies on atomic bomb survivors and their offspring, which have reported persistent epigenetic and genetic changes across generations [6].

It is worth noting that some population studies, such as those conducted in Turkey and Lithuania, have also demonstrated significant associations between the Pro allele and early-onset or aggressive breast cancer phenotypes [2,8]. Conversely, a few European studies report a lack of association or even suggest a protective role for the Arg allele in certain contexts, emphasizing the importance of environmental modifiers and ethnic-specific genetic backgrounds [13].

Importantly, the genotype distribution in the control group was in Hardy–Weinberg Equilibrium, supporting the validity of genotyping and reducing the likelihood of population stratification or selection bias. The higher prevalence of GC/CC genotypes in Group C (sporadic cases) compared to controls, albeit less significant, suggests that the TP53 polymorphism may confer risk independently of known environmental or familial factors. This aligns with studies showing that even low-risk variants can contribute meaningfully in polygenic models of cancer susceptibility [10].

Despite the novelty of our findings, the study has several limitations. The sample size, while sufficient for primary associations, may not provide adequate power for detecting subtle gene–environment interactions or differences within age subgroups. The classification of radiation exposure relied on registry data and residential history, which may be subject to misclassification. Furthermore, only one polymorphism in TP53 was analyzed, while the gene harbors numerous other functional variants and haplotypes [13].

Conclusion and Perspectives

This study demonstrates a significant association between the TP53 rs1042522 (Arg72Pro) polymorphism and breast cancer risk in women from a radiation-exposed region, particularly among those with both familial and environmental risk factors. The findings support the hypothesis that gene–environment interactions contribute meaningfully to breast cancer susceptibility in historically irradiated populations.

The increased prevalence of GC/CC genotypes among breast cancer patients-especially those with combined risk profiles-suggests that genetic screening for TP53 variants may hold clinical relevance for risk stratification in exposed populations. Moreover, the study reinforces the need to consider environmental history, such as chronic radiation exposure, in genetic association studies and risk models.

Future research should aim to expand the genetic scope beyond single polymorphisms by incorporating additional loci involved in DNA repair, apoptosis, and hormonal pathways. Larger, multiethnic cohorts and longitudinal designs may further clarify the temporal dynamics and biological mechanisms underlying the interaction between inherited susceptibility and radiation exposure.

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