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The Association of rs1042522 and rs3088440 Polymorphisms with CA125, IFN-γ, and IL-10 Levels in Cervical Cancer and Genital Warts Patients

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Abstract

Introduction: Variants in tumor suppressor genes may affect susceptibility to HPV-related diseases and alter immune responses by modifying cytokine production. Thus, in the current study, we sought to examine how rs1042522 (TP53 codon 72) and rs3088440 (INK4a 540 C>T) variants correlate with serum CA125, IFN-γ, and IL-10 levels in Iraqi women with cervical cancer, genital warts, or no disease.

Methods: We enrolled 106 participants from four Iraqi hospitals (October 2024-January 2025): 26 with cervical cancer, 30 with genital warts, and 50 healthy individuals. Genetic variants were identified through PCR-RFLP, and ELISA was used to measure CA125, IFN-γ, and IL-10 in serum. We applied Chi-square tests for genotype frequencies and Kruskal-Wallis followed by Mann-Whitney U tests for biomarker analysis.

Results: For rs1042522, controls had higher GG genotype frequency (46.0%) than genital warts patients (23.3%; P=0.03), whereas genital warts patients showed increased CC genotype (43.3%). Among genital warts patients, IL-10 concentrations varied by rs1042522 genotype (P=0.025): CC carriers had elevated levels (0.76 pg/mL) versus GG carriers (0.60 pg/mL; P=0.006). The rs3088440 variant showed no meaningful associations with disease or biomarkers.

Conclusion: Our findings link rs1042522 to genital warts risk and IL-10 regulation in affected patients, indicating a genetic basis for immune responses in HPV-associated conditions. This variant may serve as a useful marker for identifying at-risk individuals.

Keywords: interleukin-10; genetic polymorphism; papillomavirus infections; p53; uterine cervical neoplasms

Introduction

Globally, cervical cancer is fourth leading cause of cancer mortality in women (1). The primary etiological agent is human papillomavirus (HPV), with HPV DNA present in roughly 93% of cervical malignancies worldwide. Two high-risk strains, HPV-16 and HPV-18, are responsible for approximately 70% of these cancers, where HPV-16 contributes to 50% and HPV-18 to 14% of cases (2,3). Beyond cervical malignancies, HPV also causes genital warts, representing another significant disease burden. Within the Middle East and North Africa (MENA) region, HPV prevalence demonstrates marked heterogeneity, spanning from 0-25% among low-risk populations to 98% in individuals with genital warts and invasive cervical disease (4). Pooled data from recent meta-analyses indicate HPV detection rates of 81% in cervical cancer cases, 54% in patients with cytological abnormalities, and 16% in the general MENA population (5). Although prophylactic vaccines exist, cervical cancer rates still elevated in developing countries where organized screening initiatives are limited or implemented only opportunistically (4,6).

Cervical cancer initiation and progression involve huge immune dysregulation, particularly affecting critical cytokines like interferon-gamma (IFN-γ) and interleukin-10 (IL-10). IFN-γ works as an anti-tumor agent and also a robust prognostic indicator. Evidence states that elevated IFN-γ correlates with positive outcomes, 93.3% of IFN-γ-positive individuals cleared high-risk HPV versus 66.7% of negative cases (7). Also, increased intra-tumoral IFN-γ mRNA predicts better survival in cervical cancer (8). Paradoxically, cervical tumors mostly exhibit reduced or undetectable IFN-γ expression, reflecting compromised cellular immunity during malignant transformation (9,10). IL-10 has dual roles in cervical carcinogenesis (11). Conventionally viewed as immunosuppressive, promoting malignancy through regulatory T cell expansion and immune tolerance (10,12); however, however, recent data show IL-10 can also support $CD8^+$ T cell viability and anti-tumor activity (13). As a result, both cytokines decline as lesions progress from precancerous stages to invasive disease, signaling a transition from immune protection to suppression (10,14). Besides these cytokines, CA125 is an important tumor marker in cervical cancer, with elevated serum levels often correlating with disease severity and prognosis (15). Thus, understanding the factors that influence these biomarker levels is essential for improving disease prediction and patient management.

In recent decades, genetic polymorphisms have emerged as important determinants of cancer susceptibility and immune response variability among individuals. The *TP53* gene, which encodes the *p53* tumor suppressor protein, contains a common polymorphism at codon 72 (rs1042522) that results in either an arginine (Arg) or proline (Pro) amino acid at this position (16). This polymorphism has been extensively studied across various cancer types, showing variable associations with cancer risk depending on ethnicity and cancer site. Meta-analyses have showed significant associations between rs1042522 and increased risk of lung, colorectal, gastric and cervical cancer, particularly in Asian, Caucasian and African populations (16–19). In cervical cancer specifically, studies have shown significantly higher frequency of certain rs1042522 genotypes in cancer samples from HPV16-infected women, suggesting this polymorphism might be associated with increased risk of cervical cancer development (20). Furthermore, this polymorphism influences the functional properties of the p53 protein, with the Arg72 variant showing greater ability to induce cell death (apoptosis) compared to the Pro72 variant (21). Besides cancer susceptibility, rs1042522 has been reported to affect mutant p53 selection in tumors and influence patient survival outcomes (22). Similarly, the *p16* gene, which plays a critical role in cell cycle regulation and tumor suppression, contains polymorphisms including rs3088440 that have been investigated in relation to cervical cancer progression (20). Although initial studies have not shown significant associations between rs3088440 and cervical cancer risk in HPV16-infected women (20), this polymorphism remains of interest due to the essential role of *p16* in cellular responses to oncogenic stimuli. Nevertheless, both genetic variants in tumor suppressor genes and immune-related genes may influence cytokine production and immune response patterns, thereby affecting the body's ability to control HPV infection and prevent cancer progression.

Despite the well-established roles of HPV infection, immune dysregulation, and genetic susceptibility in cervical cancer development, there remains a significant gap in understanding how specific genetic polymorphisms influence immune biomarker levels in patients with cervical cancer and genital warts. Therefore, to address this knowledge gap and to assess the association between rs1042522 and rs3088440 polymorphisms and serum levels of CA125, IFN-γ, and IL-10, we conducted this study in cervical cancer patients, genital warts patients, and healthy controls.

Methods

Study design and subjects

This cross-sectional observational study was conducted at Ibn Ghazwan Hospital (Cervical Cancer Unit, Basrah, Iraq), Al-Hussain Teaching Hospital at Hillah (Hillah, Iraq), Medical City (Baghdad, Iraq), and Al-Habboubi Hospital (Nasiriyah, Iraq) between October 2024 and January 2025. The study aimed to investigate the association between rs1042522 and rs3088440

polymorphisms and serum levels of CA125, IFN-γ, and IL-10 in patients with cervical cancer, genital warts, and healthy controls. The included 106 participants divided into three groups: cervical cancer patients (n=26), genital warts patients (n=30), and healthy participants (n=50).

Inclusion and exclusion criteria

The participants in cancer group were women with histologically confirmed cervical cancer diagnosed according to the International Federation of Gynecology and Obstetrics (FIGO) staging system. Patients were recruited prior to receiving any treatment (chemotherapy or radiotherapy). In addition, the genital wart group women with clinically diagnosed genital warts, confirmed by physical examination by a qualified gynecologist were included. For healthy subjects, they were apparently healthy women with no history of cervical pathology, or genital warts. The healthy controls were age-matched with the case groups and were recruited from individuals attending routine gynecological check-ups. All participants gave informed consent. Those with other malignancies or autoimmune diseases, chronic inflammatory conditions, current use of immunosuppressive medications or hormonal therapy, pregnancy or lactation or who refused to participate in the study were all excluded.

Blood sampling

Following informed consent, 5 mL of venous blood was collected from each participant using sterile disposable syringes (Al-Rawabi Inject, China) under aseptic conditions. Blood samples were collected in gel tubes (Jiangsu Xinkang, China) and allowed to clot at room temperature for 30 minutes. Samples were then centrifuged using an ordinary centrifuge (Hettich, Germany) at 3000 rpm for 10 minutes to separate serum. The separated serum was aliquoted into sterile Eppendorf tubes (1.5 mL, Almalak, China) and stored at -20°C (Alhafidh Deep Freezer, China) until further analysis. All samples were transported in a cool box (Hepo, China) to maintain the cold chain.

Immunological analysis

Serum concentrations of IL-10, IFN-γ and CA125 were measured using enzyme-linked immunosorbent assay (ELISA) kits (Reed Biotech, China) according to the manufacturer's instructions. All kits were stored at 2–8°C prior to use. All samples were analyzed in duplicate, and the mean values were used for statistical analysis. The ELISA system (BioTek, USA) included an automated reader, washer, and printer to ensure accurate and reproducible results.

Genetic analysis

Genomic DNA was extracted from peripheral blood leukocytes using the salting-out method and quantified spectrophotometrically at 260/280 nm using a NanoDrop spectrophotometer. The genes of interest were amplified using polymerase chain reaction (PCR) with primers synthesized by Macrogen Co., Ltd. (Seoul, South Korea). For *TP53* (codon 72), the forward primer was 5′-TCCCCCTTGCCGTCCCAA-3′ and the reverse primer was 5′-CGTGCAAGTCACAGACTT-3′. For *INK4a* (540C>T), the forward primer was 5′-GACTCTGAGGGGCTGGA-3′ and the reverse primer was 5′-GGTCCTGTTGCTGTGCTT-3′. PCR amplification was performed in a 25 μL reaction volume containing genomic DNA template, PCR master mix, and respective primers. For rs1042522, the PCR conditions included initial denaturation at 95°C for 5 minutes, followed by 35 cycles of 95°C for 30 seconds, 58°C for 30 seconds, and 72°C for 45 seconds, with a final extension at 72°C for 5 minutes. For rs3088440, the annealing temperature was adjusted to 54°C, while other conditions remained identical.

The rs1042522 (*TP53* codon 72) polymorphism was detected using PCR-RFLP method. The 421 bp amplified fragment was digested with BstFNI restriction enzyme (New England Biolabs, USA) at 37°C for 4 hours, yielding genotype-specific patterns: GG (421 bp), GC (421, 217, 204 bp), and CC (217, 204 bp). The rs3088440 (*p16*/*INK4a*) polymorphism was genotyped by digesting the 143 bp amplified fragment with HaeIII restriction enzyme (New England Biolabs, USA) at 37°C for 4 hours, producing patterns: CC (143 bp), CT (143, 107, 36 bp), and TT (107, 36 bp). All digested products were separated by 2% agarose gel electrophoresis at 100V for 60 minutes, stained with ethidium bromide, and visualized under UV transillumination. A 100 bp DNA ladder was used as a molecular size marker for fragment identification.

Statistical analysis

All statistical analyses were conducted using GraphPad Prism 10.0. For continuous data, we reported mean ± standard deviation (SD) when normally distributed and median with interquartile range (IQR) for non-normal distributions. Group comparisons were made with one-way ANOVA for parametric data and Kruskal-Wallis testing for non-parametric data. When significant differences found, we applied Mann-Whitney U tests with Bonferroni adjustment for post-hoc pairwise analyses. Categorical data reported as counts and percentages, with group differences evaluated through chi-square analysis or Fisher's exact test depending on expected cell frequencies. We verified Hardy-Weinberg equilibrium for genotype distribution in controls using chi-square goodness-of-fit analysis. To examine genotype-biomarker relationships, we used Mann-Whitney U tests for two-genotype comparisons and Kruskal-Wallis tests for three-genotype comparisons. Separate subgroup analyses were conducted for each clinical category (cancer patients, warts patients, and controls). Statistical significance was set at $p<0.05$ for all two-tailed tests.

Results

The demographic characteristics of participants are presented in **Table 1**. Across the groups, the age differed significantly among the three study groups (P<0.001). The cervical cancer group was significantly older with a median age of 40.0 (IQR: 35.0-47.0) years compared to both the control group (33.5 years, IQR: 26.0-38.0) and genital warts group (28.0 years, IQR: 24.0-32.8), while the control and genital warts groups showed no significant age difference from each other. In addition, family history of cancer was reported in 14.0% (7/50) of controls, 20.0% (6/30) of genital warts patients, and 23.1% (6/26) of cervical cancer patients, with no statistically significant differences observed among the groups (P=0.583).\

Table 1. Age and family history findings of participants with complete genotype data (N=106).

Characteristic	Control (n=50)	Genital warts (n=30)	Cervical cancer (n=26)	*P*-value
Age (years)	33.5 (26.0-38.0)[a]	28.0 (24.0-32.8)[a]	40.0 (35.0-47.0)[b]	**<0.001**
Family history of cancer	7 (14.0%) [a]	6 (20.0%) [a]	6 (23.1%) [a]	0.583

Note: Data are presented as median (interquartile range) for continuous variables and as frequency (percentage) for categorical variables. Bold *P*-values denote statistical significance (P<0.05). Values with different superscript letters within the same row are significantly different from each other (P<0.05) based on post-hoc pairwise comparisons. Values sharing the same letter are not significantly different. *P*-values calculated using Kruskal-Wallis test for continuous variables and Chi-square test for categorical variables.

The distribution of genetic polymorphisms among study participants is presented in **Figure 2**. For the rs1042522 polymorphism (TP53 codon 72, Arg72Pro), a statistically significant difference was observed in genotype distribution between control and genital warts groups (P=0.030), with the GG genotype being significantly more frequent in controls (46.0%, 23/50) compared to genital warts patients (23.3%, 7/30). The CC genotype showed an inverse pattern, occurring more frequently in the genital warts group (43.3%, 13/30) than in controls (18.0%, 9/50). However, no significant differences were detected between control and cervical cancer groups (P=0.263) or between genital warts and cervical cancer groups (P=0.426), with an overall comparison yielding a *P*-value of 0.076. In contrast, the rs3088440 polymorphism (*INK4a* 540 C>T) demonstrated no significant associations with disease status across all comparisons (overall P=0.725). The CT heterozygous genotype was most prevalent in controls (48.3%, 29/60) and cervical cancer patients (50.0%, 13/26), while the TT homozygous genotype was most frequent in genital warts patients (46.7%, 14/30), though these differences were not statistically significant.

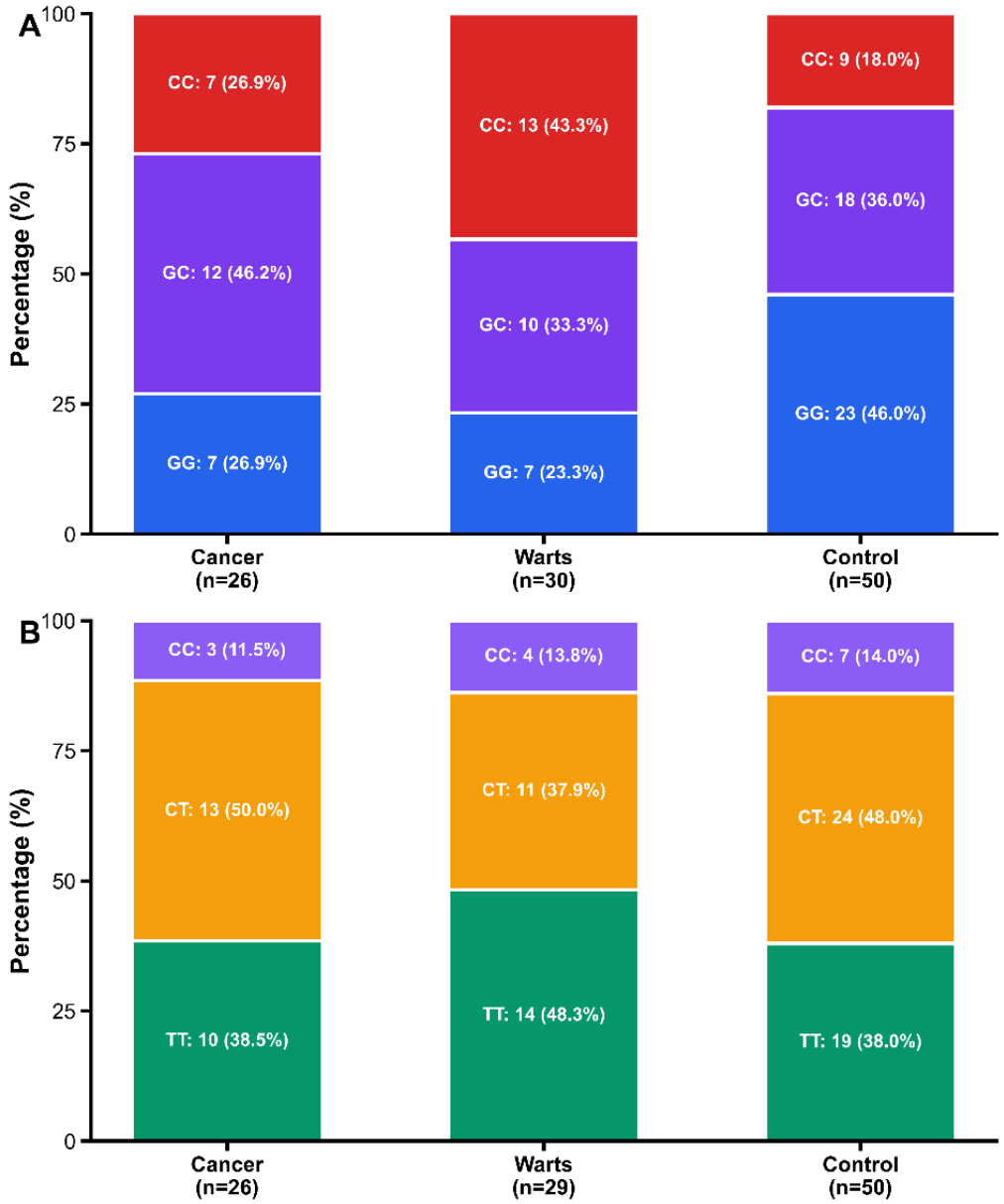

Figure 1. Stacked bar charts showing genotype frequencies for: A) rs1042522 and B) rs3088440 in cervical cancer patients (n=26), genital warts patients (n=30), and healthy participants (n=50). For rs1042522, the GG genotype was significantly more common in controls (46.0%) compared to cancer (26.9%) and warts (23.3%) groups, while the C allele frequency was elevated in disease groups (χ^2 test, p=0.042). No significant difference in genotype distribution was observed for rs3088440 (p=0.326). Numbers within bars represent absolute counts and percentages. Statistical significance was assessed using Chi-square test for genotype distributions.

The association between genetic polymorphisms and serum levels of CA125, IFN-γ and IL-10 was evaluated overall and grouped by patient health status. For the rs1042522 polymorphism in the overall analysis regardless of health status (**Figure 2**), no statistically significant differences in CA125, IFN-γ, or IL-10 levels were observed across genotypes (all P>0.05). Group-based analysis, however, revealed genotype-specific effects within the genital warts group (**Figure 3**). In genital warts patients, CA125 levels showed no significant differences across genotypes (GG: 36.61 U/mL, IQR 29.70-45.54; GC: 28.19 U/mL, IQR 18.68-39.88; CC: 37.93 U/mL, IQR 33.05-48.14; P=0.1106), nor did IFN-γ levels (GG: 48.77 pg/mL, IQR 27.25-74.26; GC: 50.01 pg/mL, IQR 26.80-93.50; CC: 45.03 pg/mL, IQR 22.71-75.56; P=0.929). However, IL-10 levels differed significantly across rs1042522 genotypes (P=0.025), with CC

genotype carriers showing significantly elevated levels (median 0.76 pg/mL, IQR 0.66-0.92) compared to GG carriers (median 0.60 pg/mL, IQR 0.49-0.62; *P*=0.006), while GC carriers exhibited intermediate levels (median 0.66 pg/mL, IQR 0.55-0.79). In the cervical cancer group (**Figure 4**), CA125 levels were similar across genotypes (GG: 62.80 U/mL, IQR 32.45-70.35; GC: 48.95 U/mL, IQR 41.85-62.70; CC: 53.30 U/mL, IQR 33.40-123.05; *P*=0.989), while IFN-γ showed a non-significant trend toward higher levels in GC (69.16 pg/mL, IQR 20.02-90.43) and CC (58.60 pg/mL, IQR 37.09-107.94) carriers compared to GG carriers (11.23 pg/mL, IQR 9.84-37.46; *P*=0.098). IL-10 levels in cervical cancer patients were comparable across all rs1042522 genotypes (GG: 0.59 pg/mL, IQR 0.58-0.65; GC: 0.66 pg/mL, IQR 0.56-0.72; CC: 0.64 pg/mL, IQR 0.60-0.73; *P*=0.821). For the rs3088440 polymorphism, no significant associations were found between genotypes (CC, CT, TT) and any biomarker levels when analyzing all participants collectively (**Figure 5**; all *P*>0.05), suggesting that this polymorphism does not considerably influence circulating levels of these biomarkers in this cohort.

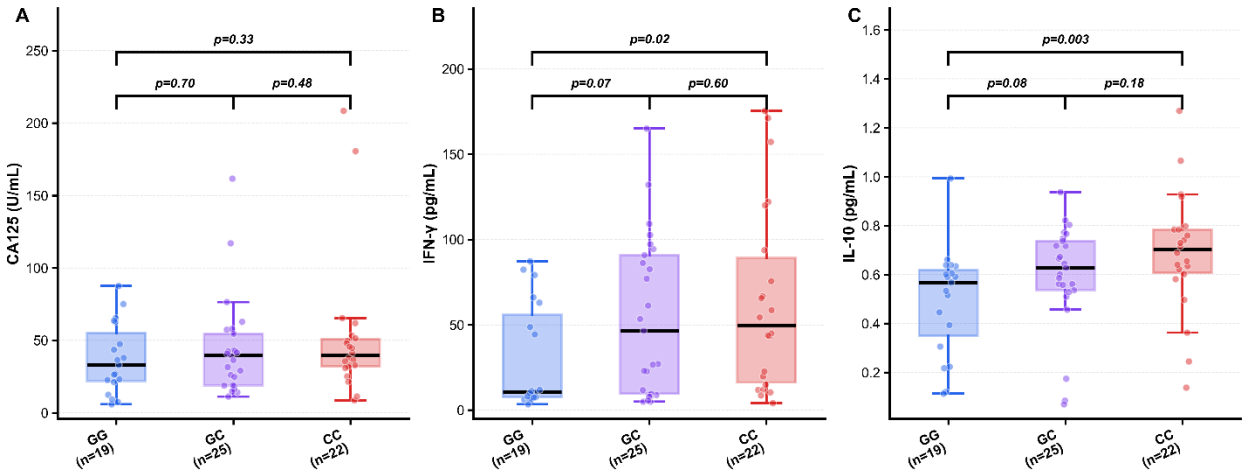

Figure 2. Tumor marker CA125, IFN-γ and IL-10 concentrations among participants (overall and regardless of health status) based on genotype of the *TP53* variant (rs1042522). The plot presents median (IQR) of serum levels of the tested markers, with the black horizontal line denote the median.

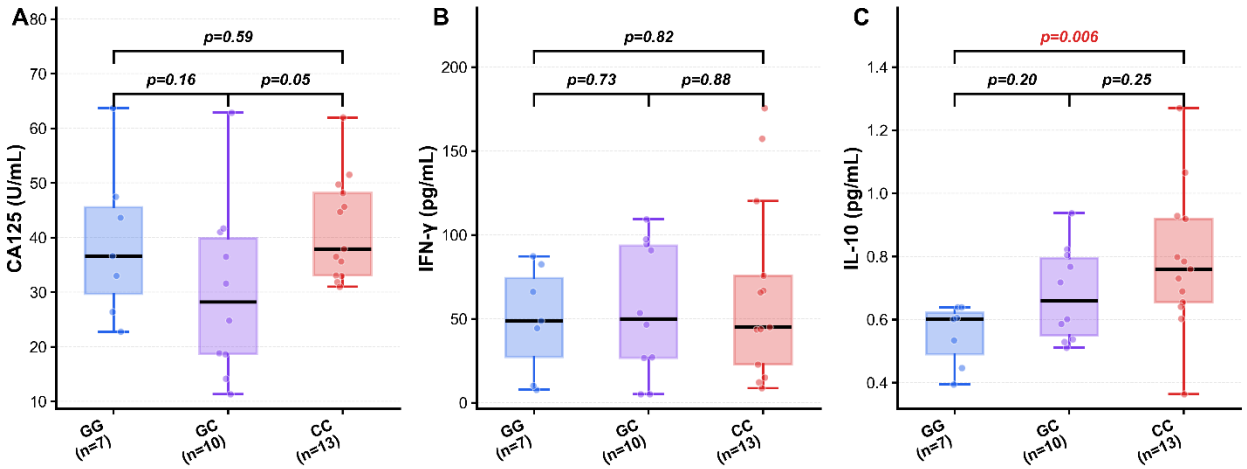

Figure 3. Tumor marker CA125, IFN-γ and IL-10 concentrations among patients with wart based on genotype of the *TP53* variant (rs1042522). The plot presents median (IQR) of serum levels of the tested markers, with the black horizontal line denote the median.

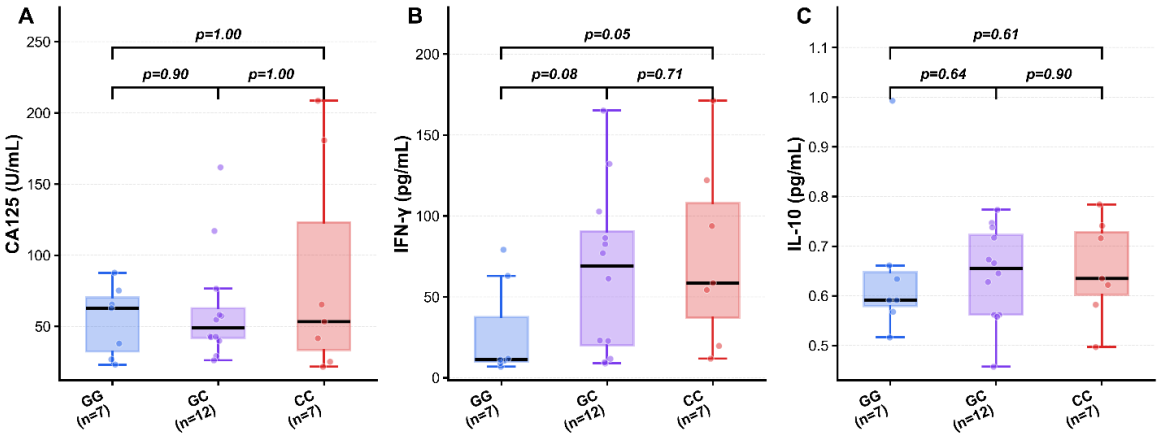

Figure 4. Tumor marker CA125, IFN-γ and IL-10 concentrations among cervical cancer patients based on genotype of the *TP53* variant (rs1042522). The plot presents median (IQR) of serum levels of the tested markers, with the black horizontal line denote the median.

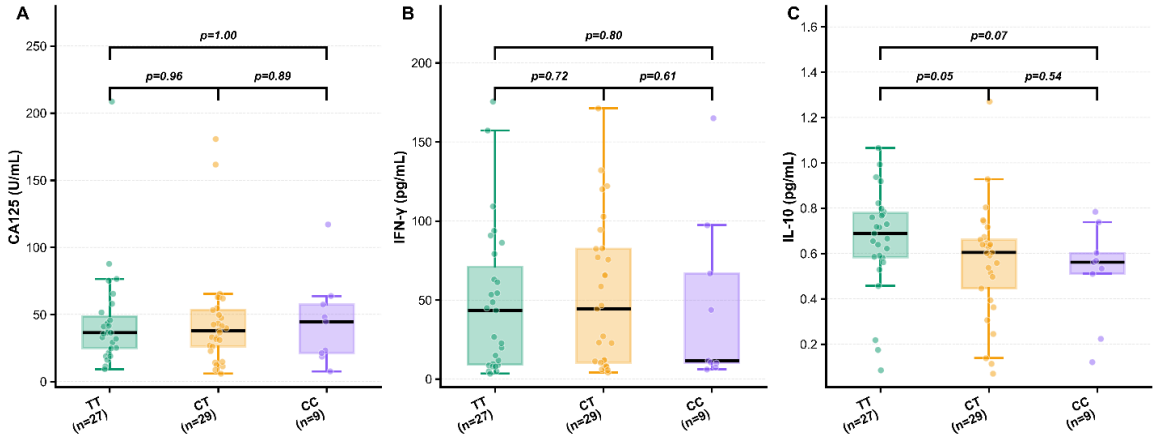

Figure 5. Tumor marker CA125, IFN-γ and IL-10 concentrations among participants (overall and regardless of health status) based on genotype of the *INK4a* variant (rs3088440). The plot presents median (IQR) of serum levels of the tested markers, with the black horizontal line denote the median.

Discussion

Our study found that cervical cancer patients were significantly older (median 40 years) than both control and genital warts groups, which agrees with previous local and regional research showing that cervical cancer is most common in women aged 43-52 years (23). This age difference reflects the natural progression of HPV-related disease, where initial infections and genital warts occur in younger women while malignant transformation develops later after prolonged viral persistence. Regarding family history of cancer, we found that 14-23% of participants across all groups reported having family members with cancer, with no significant differences between groups. This is also consistent with international studies reporting 22% prevalence of family cancer history in cervical cancer patients (24).

In addition, we found that the rs1042522 polymorphism showed a significant association with genital warts but not cervical cancer, with the GG genotype being more protective in controls (46.0%) compared to genital warts patients (23.3%), while the CC genotype was more frequent in genital warts (43.3%). This finding is particularly interesting given that previous research on this polymorphism has yielded mixed results across different populations and disease stages. While several studies found no overall association between this polymorphism and cervical cancer risk (25–27), a large meta-analysis revealed that the G/Arg variant significantly increased the odds of progression from precancerous lesions to invasive cervical cancer specifically in HPV-positive individuals (28), and similar findings were reported in HPV-positive women from Kyrgyzstan (29) and Montreal (30). Interestingly, the only previous Iraqi study on this polymorphism found that the C/Pro allele was associated with

increased breast cancer risk (31), suggesting that this genetic variant may have different effects depending on the cancer type and population studied. The lack of association between rs1042522 and cervical cancer in our study might be explained by the disease stage, as our cervical cancer patients had already progressed to invasive disease, whereas the association appears strongest during the transition from precancerous lesions to cancer. For the rs3088440 polymorphism (INK4a 540 C>T), we found no significant associations with any disease group, which aligns with a Thai study that also reported no association between this *p16* gene polymorphism and cervical cancer risk in HPV16-infected women (20), suggesting this variant may not play a major role in HPV-related disease susceptibility across different populations.

This study discovered a notable association between the rs1042522 polymorphism and IL-10 levels specifically in the genital warts group, where carriers of the CC (Pro/Pro) genotype had significantly higher IL-10 levels (0.76 pg/mL) compared to GG (Arg/Arg) carriers (0.60 pg/mL), while no such associations were observed in the overall analysis or in cervical cancer patients. This genotype-specific effect on IL-10 levels is biologically reasonable, as previous research has demonstrated that genetic variants in immune-related genes can significantly alter cytokine production and serum levels. Several studies have shown that *IL-10* gene polymorphisms can influence IL-10 expression, with Singhal et al. (2015) reporting that the GTC haplotype was associated with higher serum IL-10 levels and increased cervical cancer risk, and Zidi et al. (2015) finding that certain IL-10 genotypes resulted in reduced IL-10 serum levels (32,33). The elevated IL-10 in CC genotype carriers with genital warts is particularly interesting because IL-10 is an immunosuppressive cytokine that can dampen antiviral immune responses, potentially facilitating HPV persistence and disease progression. Multiple studies have established that IL-10 polymorphisms modify cervical cancer susceptibility by altering immune responses, with variants like IL-10 -592C/A and -819C/T significantly increasing cervical cancer risk, particularly in Asian populations (34–36). The absence of significant associations in our cervical cancer group might reflect the fact that by the time disease has progressed to invasive cancer, other factors beyond individual genetic variants become more dominant in determining cytokine levels. Our finding that rs3088440 showed no associations with any biomarkers aligns with the limited evidence for this polymorphism's functional impact on immune markers, suggesting it may not play a major role in modulating inflammatory responses in HPV-related diseases.

Although it reports new findings from our population, this study still has several limitations. The relatively small sample size, particularly for cervical cancer patients (n=26), may have limited statistical power to detect associations. The cross-sectional design precludes causal inferences between genetic polymorphisms and disease outcomes. Our findings may not be generalizable to other ethnic populations. Additionally, we did not assess other important risk factors such as smoking status and sexual behavior, which could confound the observed associations. Future larger studies incorporating HPV genotyping and comprehensive risk factor assessment are needed to validate these findings.

Conclusion

This study concludes that the rs1042522 polymorphism is significantly associated with genital warts susceptibility, with the GG genotype showing a protective effect. Importantly, we identified a genotype-specific association between rs1042522 and IL-10 levels in genital warts patients, where CC genotype carriers exhibited significantly elevated IL-10 levels, suggesting a potential mechanism for HPV persistence through immune modulation. However, rs3088440 showed no significant associations with disease status or biomarker levels. These findings highlight the importance of genetic polymorphisms in modulating immune responses in HPV-related diseases and suggest that rs1042522 genotyping may have potential clinical utility in risk stratification for HPV-related conditions. Further large-scale studies incorporating HPV genotyping are required to confirm these findings and explore their medical applications.

Statement of Ethics: Authors should show that studies involving Human Participants were planned, conducted and reported in accordance with The World Medical Association (WMA) Declaration of Helsinki.

Ethical Approval: This study was approved by the Institutional Committee of the Faculty of Science of the University of Al-Qadisiyah (Approval number: #188/2024, dated 20-Aug-2024). All participants provided written informed consent prior to enrollment.

Informed Consent Statement: All included participants, in the current study, gave informed consent before enrollment.

Data Sharing Statement: Date sets are Not available publicly because of legal and privacy/policy reasons. However, its available by request from the Correspondence Author.

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