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IMPACT OF P21 SER31ARG AND TP53 ARG72PRO POLYMORPHISMS ON HPV SUSCEPTIBILITY AND CERVICAL LESION SEVERITY

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ABSTRACT

Introduction: Although preventable and treatable, Uterine Cervical Cancer (UCC) continues to claim lives every year. Even though Human Papillomavirus (HPV) is the main etiological agent of this disease, single nucleotide polymorphisms (SNPs) in genes involved in cell cycle control, such as *P21* and *TP53*, are important factors in cancer development.

Objective: This retrospective case-control study aimed to investigate the association of the *P21* Ser31Arg (rs1801270) and *TP53* Arg72Pro (rs1042522) polymorphisms with HPV infection persistence and with the progression of Cervical Intraepithelial Neoplasia (CIN I) to High-Grade Squamous Intraepithelial Lesions (HSIL) to UCC.

Methods: We analyzed 581 women, including 282 cases (HPV ^{positive}, with CIN/ UCC) and 299 controls (HPV ^{negative}, without CIN). Samples from the case group were obtained from paraffin- embedded histological tissues, while control samples were collected from vaginal secretions immersed in saline solution. The rs1801270 SNP was evaluated using the Polymerase Chain Reaction-Restriction Fragment Length Polymorphism (PCR-RFLP), and the rs1042522 SNP was analyzed using the Mismatch Amplification Mutation Assay-PCR (MAMA-PCR).

Results: The *P21* rs1801270 polymorphism was significantly associated with increased risk of HPV persistence and CIN. Individuals with CA (OR = 2.23; 95% CI: 1.366–3.650; $p < 0.0001$) and AA (OR = 3.87; 95% CI: 2.455–6.113; $p < 0.0001$) genotypes showed increased CIN/UCC risk. Although no link with HSIL was found individually, CA+AA (OR = 3.14; 95% CI: 2.04–4.83; $p = 7.57\times10^{-8}$) suggests A allele triples risk. *TP53* rs1042522 was associated with HPV: GC (OR = 2.45; 95% CI: 1.632–3.682; $p < 0.0001$), CC (OR = 1.74;

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95% CI: 1.168–2.597; p < 0.0001), but CC was protective against HSIL (OR = 0.049; 95% CI: 0.023–0.103; p < 0.0001). GC+CC vs GG confirmed C allele increases HPV risk (OR = 2.06; 95% CI: 1.48–2.87; p = 2.17×10^{-5}), yet may protect against HSIL.

Conclusion: our results indicate that the *P21* rs1801270 and *TP53* rs1042522 polymorphisms are associated with persistent HPV infection and NIC I. The *P21* A allele increased CIN risk, while the TP53 C allele was linked to HPV susceptibility; the CC genotype showed a protective effect against HSIL. These results highlight the relevance of genetic polymorphisms as molecular markers capable of fostering more accurate risk stratification and guiding clinical practices.

Keywords: Uterine Cervical Cancer (UCC). Single Nucleotide Polymorphism (SNP). *Cyclin-dependent kinase inhibitor 1A (P21)*. *Tumor protein P53* (P53). Polymorphisms.

IMPACTO DOS POLIMORFISMOS P21 SER31ARG E TP53 ARG72PRO NA SUSCETIBILIDADE AO HPV E NA GRAVIDADE DAS LESÕES CERVICAIS

RESUMO

Introdução: Embora seja prevenível e tratável, o câncer do colo do útero (CCU) continua causando mortes todos os anos. Apesar de o Papilomavírus Humano (HPV) ser o principal agente etiológico dessa doença, polimorfismos de nucleotídeo único (SNPs) em genes envolvidos no controle do ciclo celular, como P21 e TP53, são fatores importantes no desenvolvimento do câncer.

Objetivo: Este estudo retrospectivo caso-controle teve como objetivo investigar a associação dos polimorfismos P21 Ser31Arg (rs1801270) e TP53 Arg72Pro (rs1042522) com a persistência da infecção pelo HPV e com a progressão da Neoplasia Intraepitelial Cervical (NIC I) para Lesões Intraepiteliais Escamosas de Alto Grau (HSIL) até o CCU.

Métodos: Foram analisadas 581 mulheres, sendo 282 casos (HPV positivo, com NIC/CCU) e 299 controles (HPV negativo, sem NIC). As amostras do grupo caso foram obtidas de tecidos histológicos embebidos em parafina, enquanto as amostras do grupo controle foram coletadas a partir de secreções vaginais imersas em solução salina. O SNP rs1801270 foi avaliado por PCR-RFLP (Reação em Cadeia da Polimerase com Polimorfismo de Fragmento de Restrição), e o SNP rs1042522 foi analisado por MAMA-PCR (PCR com Amplificação de Mutações por Incompatibilidade de Pareamento).

Resultados: O polimorfismo P21 rs1801270 foi significativamente associado ao aumento do risco de persistência do HPV e de desenvolvimento de NIC. Indivíduos com os genótipos CA (OR = 2,23; IC 95%: 1,366–3,650; p < 0,0001) e AA (OR = 3,87; IC 95%: 2,455–6,113; p < 0,0001) apresentaram risco aumentado para NIC/CCU. Embora não tenha sido observada associação individual com HSIL, CA+AA (OR = 3,14; IC 95%: 2,04–4,83; p = $7,57\times10^{-8}$) sugerem que o alelo A triplica o risco. O polimorfismo TP53 rs1042522 foi associado ao HPV: GC (OR = 2,45; IC 95%: 1,632–3,682; p < 0,0001), CC (OR = 1,74; IC 95%: 1,168–2,597; p < 0,0001), mas CC foi protetor contra HSIL (OR = 0,049; IC 95%: 0,023–0,103; p < 0,0001). A comparação GC+CC *vs* GG confirmou que o alelo C aumenta o risco para HPV (OR = 2,06; IC 95%: 1,48–2,87; p = $2,17\times10^{-5}$), embora possa proteger contra HSIL.

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Conclusão: Nossos resultados indicam que os polimorfismos P21 rs1801270 e TP53 rs1042522 estão associados à infecção persistente por HPV e à NIC I. O alelo A do P21 aumentou o risco para NIC, enquanto o alelo C do TP53 esteve associado à suscetibilidade ao HPV, sendo que o genótipo CC mostrou efeito protetor contra HSIL. Esses achados destacam a relevância dos polimorfismos genéticos como marcadores moleculares capazes de fomentar uma estratificação de risco mais precisa e orientar condutas clínicas.

Palavras-chave: Câncer do Colo do Útero (CCU). Polimorfismo de Nucleotídeo Único (SNP). *Inibidor de quinase dependente de ciclina 1A (P21). Proteína supressora de tumor tp53 (p53).* Polimorfismos.

IMPACTO DE LOS POLIMORFISMOS P21 SER31ARG Y TP53 ARG72PRO EN LA SUSCEPTIBILIDAD AL VPH Y LA GRAVEDAD DE LAS LESIONES CERVICALES

RESUMEN
Introducción: Aunque es prevenible y tratable, el cáncer de cuello uterino (CAC) continúa causando muertes cada año. Aunque el Virus del Papiloma Humano (VPH) es el principal agente etiológico de esta enfermedad, los polimorfismos de un solo nucleótido (SNP) en genes involucrados en el control del ciclo celular, como P21 y TP53, son factores importantes en el desarrollo del cáncer.

Objetivo: Este estudio retrospectivo de casos y controles tuvo como objetivo investigar la asociación de los polimorfismos P21 Ser31Arg (rs1801270) y TP53 Arg72Pro (rs1042522) con la persistencia de la infección por VPH y con la progresión de la neoplasia intraepitelial cervical (NIC I) a lesiones intraepiteliales escamosas de alto grado (HSIL) hasta CC.

Métodos: Se analizaron 581 mujeres, 282 casos (HPV positivos, con CIN/CC) y 299 controles (HPV negativos, sin CIN). Las muestras del grupo de casos se obtuvieron de tejidos histológicos incluidos en parafina, mientras que las muestras del grupo de control se recolectaron de secreciones vaginales sumergidas en solución salina. El SNP rs1801270 se evaluó mediante PCR-RFLP (reacción en cadena de la polimerasa con polimorfismo de longitud de fragmentos de restricción) y el SNP rs1042522 se analizó mediante MAMA-PCR (PCR con amplificación de mutaciones por desajuste de pares).

Resultados: El polimorfismo P21 rs1801270 se asoció significativamente con un mayor riesgo de persistencia del VPH y desarrollo de CIN. Los individuos con genotipos CA (OR = 2,23; IC del 95 %: 1,366–3,650; p < 0,0001) y AA (OR = 3,87; IC del 95 %: 2,455–6,113; p < 0,0001) tuvieron un mayor riesgo de presentar CIN/CC. Aunque no se observó asociación individual con HSIL, CA+AA (OR = 3,14; IC del 95 %: 2,04-4,83; p = $7{,}57\times10^{-8}$) sugiere que el alelo A triplica el riesgo. El polimorfismo TP53 rs1042522 se asoció con HPV: GC (OR = 2,45; IC del 95 %: 1,632–3,682; p < 0,0001), CC (OR = 1,74; IC del 95 %: 1,168–2,597; p < 0,0001), pero CC fue protector contra HSIL (OR = 0,049; IC del 95 %: 0,023–0,103; p < 0,0001). La comparación GC+CC vs GG confirmó que el alelo C aumenta el riesgo de VPH (OR = 2,06; IC del 95 %: 1,48-2,87; p = $2{,}17\times10^{-5}$), aunque puede proteger contra HSIL.

Conclusión: Nuestros resultados indican que los polimorfismos P21 rs1801270 y TP53 rs1042522 están asociados con la infección persistente por VPH y CIN I. El alelo P21 A

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aumentó el riesgo de CIN, mientras que el alelo TP53 C se asoció con la susceptibilidad al VPH y el genotipo CC mostró un efecto protector contra HSIL. Estos hallazgos resaltan la relevancia de los polimorfismos genéticos como marcadores moleculares capaces de promover una estratificación de riesgo más precisa y guiar la conducta clínica.

Palabras clave: Cáncer de Cuello Uterino (CC). Polimorfismo de Nucleótido Único (SNP). *Inhibidor de la quinasa dependiente de ciclina 1A (P21). Proteína supresora de tumores tp53 (p53).* Polimorfismos.

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1 INTRODUCTION

Globally, Uterine Cervical Cancer (UCC) is the fourth most common cancer among women (INCA, 2022). The highest incidence rates occur in Sub-Saharan Africa, Central America, and Southeast Asia (GCO.ORG, 2020; WHO, 2022; WHO, 2024a).

Human Papillomavirus (HPV) is detected in approximately 90% of UCC cases (FOWLER et al. 2022). To date, more than 200 HPV types have been identified, with at least 14 of them classified as oncogenic. Among these, types 16 and 18 are the most prevalent, found in about 70% of UCC cases, followed by genotypes 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68 (NCI, 2025). However, the high prevalence of HPV infection compared to the relatively low incidence of UCC suggests that other factors, including genetic predisposition, significantly influence not only HPV infection control but also the progression from Cervical Intraepithelial Neoplasia (CIN) to UCC (WHO 2024b; ACS.ORG 2023).

In this context, the integrity of the *Cyclin-Dependent Kinase Inhibitor 1A (P21)* and *Tumor Protein 53 (TP53)* genes - encoding the proteins p21 and p53, respectively - is crucial for cell cycle regulation (YANG et al. 2004; GONG, 2010; CHEN, 2016). These proteins act synergistically by forming complexes, recruiting other proteins, and consequently regulating the cell cycle while contributing to DNA repair. For instance, the P53-P21-DREAM complex negatively regulates the transcription of genes essential for cell cycle progression, resulting in cell cycle arrest at the G1/S transition to allow DNA repair or, if necessary, induction of apoptosis (AGRAWAL and SENGUPTA, 2025; ENGELAND et al. 2018).

Additionally, during the G2 to M phase transition, p53 halts cell cycle progression by repressing the expression of cyclin B1 (CCNB1) and activating p21, which inhibits CDK1, thereby preventing the formation of the cyclin B1–CDK1 complex. This mechanism blocks mitotic entry, allowing sufficient time for DNA repair before cell division (SHENG et al. 2019).

Thus, polymorphisms in *P21* (rs1801270) and *TP53* (rs1042522) can alter the structure, function, and expression of their encoded proteins, disrupting normal cell cycle control (MACEDO et al. 2003). Although several studies have reported associations between these polymorphisms and CIN progression to UCC, findings remain conflicting (ZENG et al. 2017; WU et al. 2004).

Considering that UCC is typically preceded by CIN grades I, II, and III, this study aimed to investigate the role of SNPs rs1042522 and rs1801270 in the progression of CIN to uterine cervical cancer in women from the state of Pernambuco, Brazil.

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2 STUDY POPULATION

This study included a total of 581 women from the state of Pernambuco, Brazil, comprising individuals diagnosed with persistent HPV infection and cervical lesions (CIN I, II, and III) between 2000 and 2012, as well as women without HPV infection or cervical lesions. Samples from the experimental group were collected at the Municipal Public Health Laboratory of the Recife Health Department (LMSP/SS – Recife, PE), while control group samples were selected from the biobank of the Federal Rural University of Pernambuco (UFRPE). The experimental group consisted of 282 participants, from whom paraffin-embedded uterine tissue samples were obtained from patients diagnosed with CIN I, II, III, or uterine cervical cancer. The control group included 299 participants, from whom vaginal secretion samples preserved in saline solution were used.

2.1 ELIGIBILITY CRITERIA

Eligibility criteria for sample inclusion were: (1) availability and integrity of the stored biological material, and (2) presence of consistent epidemiological data, specifically age and ethnicity, in the patient records. Only samples that met both conditions were included in the analysis.

3 METHODOS

This retrospective study was conducted in accordance with the ethical guidelines established by the Brazilian National Health Council (Resolutions CNS No. 466/2012 and No. 510/2016) and was approved by the Research Ethics Committee (CEP) of the Federal Rural University of Pernambuco (UFRPE).

Genotyping was performed for two polymorphisms: rs1801270 in the *CDKN1A (P21)* gene and rs1042522 in the *TP5*3 gene, following protocols adapted respectively from Lima et al (2016) and Gui- Cen et al (2019).

3.1 DNA EXTRACTION

From paraffin-embedded uterine tissue using 10 histological sections of 10 µm thickness, totaling approximately 50 mg of tissue. Samples were deparaffinized by adding 1 µL of xylene to each Eppendorf tube containing the tissue section. The tubes were vortexed briefly and then incubated in a water bath at 56 °C for 1 hour. After incubation, the xylene

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was discarded, and the procedure was repeated four additional times, for a total of five xylene washes. Following deparaffinization, samples were washed sequentially with 70%, 80%, and 90% ethanol to remove residual xylene and prepare the samples for DNA extraction. The protocol was adapted based on the DNA cleaning and extraction procedure from paraffin-embedded tissues provided by the Federal University of Rio de Janeiro (UFRJ, 2025).

DNA extraction was performed using the Wizard-kit (Promega), following the Kit protocol for both paraffin-embedded samples and vaginal secretion samples stored in saline solution.

3.2 PCR TO HPV DETECTION

PCR amplification was carried out using Green Master Mix (Promega) in a final reaction volume of 15 µL. Each PCR tube contained 7.5 µL of Green Master Mix, 0.5 µL of each primer MY09 and MY11 (10 µM), 5.0 µL of genomic DNA (~50–100 ng), and 1.5 µL of nuclease-free water. The cycling conditions were as follows: initial denaturation at 95 °C for 5 minutes; 35 cycles of denaturation at 94 °C for 30 seconds, annealing at 55 °C for 30 seconds, and extension at 72 °C for 1 minute; followed by a final extension at 72 °C for 7 minutes, (Table 1).

Table 1

Primer sequences, expected band size, and interpretation for HPV detection

Primers	Primer Sequence (5′→3′)	Target Region	Band Size	Interpretation
MY09	CGTCCMARRGGAWACTGATC	L1 (consensus)	~450 bp	Band present: HPV- positive
MY11	GCMCAGGGWCATAAYAATGG	L1 (consensus)		No band: HPV-negative (if positive control amplifies)

Protocol: adapted from Pitta et al., (2010).

3.3 PCR TO HPV DETECTION

PCR products were resolved by electrophoresis on a 1.5% agarose gel stained with GelRed and visualized under UV light. Samples showing a ~450 bp band were considered HPV-positive. Samples without amplification were considered HPV-negative. Each PCR run included a known HPV-positive DNA as a positive control and a no-template (MIX) negative control to check for contamination.

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3.4 CDKN1A (CYCLIN-DEPENDENT KINASE INHIBITOR 1A, P21) PCR AND GENOTYPING

PCR amplification of a 272 bp fragment was conducted using the primers: sense (5′-GTCAGAACCGGCTGGGGATG-3′) and antisense (5′-CTCCTCCCAACTCATCCCGG-3′). The cycling conditions included an initial denaturation at 95 °C for 5 minutes; 35 cycles at 94 °C for 30 seconds, 60 °C for 30 seconds, and 72 °C for 30 seconds; followed by a final extension at 72 °C for 5 minutes.

Following PCR amplification, the products were resolved by electrophoresis on a 1.5% agarose gel. Samples exhibiting weak or unclear bands underwent a nested PCR using 3 µL of the initial PCR amplicons as templates, following the same protocol as the primary PCR to enhance detection sensitivity.

The amplified product was digested with BlpI and buffer according to the manufacturer's protocol (Uniscience) at 37 °C for 4 hours. Subsequently, the digestion products were subjected to electrophoresis on a 2% agarose gel at 100 V for 40 minutes, with voltage adjustments of 80 V and 100 V during the run, followed by visualization. In the presence of the C allele, two fragments of 183 and 89 bp were observed; the A allele produced a single fragment of 272 bp; and heterozygous samples (A/C) showed all three fragments (272, 183, and 89 bp).

3.5 TP53 (TUMOR PROTEIN TP53) GENOTYPING

PCR genotyping was performed using the Mismatch Amplification Mutation Assay-PCR (MAMA-PCR). The primers used were two allele-specific forward primers—F1 (5′-CAGAGGCTGCTCCCCG-3′) and F2 (5′-CAGAGGCTGCTCCCCC-3′)—and a common reverse primer (5′-AGCCAAGGAATACACGTGGA-3′). PCR conditions consisted of 35 cycles at 98 °C for 10 seconds, 57 °C for 30 seconds, and 72 °C for 1 minute.

All amplified products were then subjected to electrophoresis on a 1.5% agarose gel at alternating voltages of 100 V, 80 V, and 100 V for a total of 25 minutes, followed by visualization under UV light. The presence of a 199 bp band indicated successful amplification. Amplification with primer F1 corresponds to the detection of allele G, while amplification with primer F2 corresponds to allele C. Samples showing amplification with both primers were considered heterozygous (G/C), (Table 2).

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Table 2

Primer sequences, PCR conditions, and post-PCR processing for genotyping rs1801270 (P21) and rs1042522 (TP53)

Gene	Primers (5′→3′)	PCR Product	Cycling Conditions	Post-PCR Treatment
P21 rs1801270	Forward: GTCAGAACCGGCTGGGGATG Reverse: CTCCTCCCACATCACCCTGG	272 bp	95°C for 5 min; 35 cycles of 94°C for 30 s, 60°C for 30 s, 72°C for 30 s; final extension at 72°C for 5 min	Digestion with B1pI at 37°C for 4 h C allele: 183 + 89 bp A allele (homozygous): 272 bp
TP53 rs1042522	F1: CAGAGGCTGCTCCCCC (G allele) F2: CAGAGGCTGCTCCCCG (C allele) Reverse: AGGCCTAGGGTAACTGGTGA	199 bp for both alleles (F1+R or F2+R)	35 cycles of 98°C for 10 s, 57°C for 30 s, 72°C for 1 min	Allele-specific amplification using MAMA-PCR

Protocol: adapted respectively from Lima et al., (2016) and Gui-Cen et al., (2019).

3.6 STATISTICAL ANALYSES

The results were statistically analyzed using Excel and Fisher's exact test performed in Python, and were correlated with previously collected clinicopathological parameters such as age and skin color, based on data available at the time of the study.

4 RESULTS

A total of 581 patients were analyzed, comprising 282 cases (experimental group) with cervical lesions and 299 controls. In the experimental group, genotypic distribution was assessed for the *P21* (rs1801270) and *P53* (rs1042522) polymorphisms.

For the *P21* gene, the AA genotype was the most frequent across all lesion categories: 56.82% in NIC1 (n = 88), 57.65% in NIC2 (n = 85), 63.95% in NIC3 (n = 86), and 60.87% in cancer (n = 23).

The CA genotype ranged from 25.58% in NIC3 to 30.43% in cancer, while the CC genotype was the least common, ranging from 8.70% (cancer) to 14.77% (NIC1).

4.1 EXPERIMENTAL GROUP

For the *P53* gene, genotype distribution varied according to lesion severity. In NIC1, the CC genotype was predominant (68.18%), whereas in NIC2 and NIC3, the GG genotype was more frequent, observed in 56.47% and 44.19% of patients, respectively. The CG genotype accounted for 15.91% in NIC1, 40.00% in NIC2, 36.05% in NIC3, and 56.52% in

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cancer. In the cancer group, only the GG (43.48%) and CG (56.52%) genotypes were identified, with no CC genotypes detected (Table 3).

Table 3

Genotype frequencies of P21 and P53 polymorphisms

Lesion Grade	n	*P21* AA (%)	*P21* CA (%)	*P21* CC (%)	*P53* CC (%)	*P53* CG (%)	*P53* GG (%)
CIN1	88	56.82	30.68	12.50	68.18	15.91	15.91
CIN2	85	57.65	27.06	15.29	3.53	40.00	56.47
CIN3	86	63.95	25.58	10.47	19.77	36.05	44.19
Cancer	23	60.87	30.43	8.70	0.00	56.52	43.48

4.2 CONTROL GROUP

In the control group (n = 299), *P21* genotypes were distributed as AA: 114 (38.13%), CA: 93 (31.10%), and CC: 92 (30.77%). For *P53*, genotypes were GG: 170 (56.86%), CC: 71 (23.75%), and CG: 58 (19.40%).

Among the 299 individuals in the control group, the *P21* (rs1801270) AA genotype was the most frequent, observed in 114 individuals (38.13%), followed by the CA genotype in 93 individuals (31.10%), and the CC genotype in 92 individuals (30.77%). Regarding the *P53* (rs1042522) polymorphism, the GG genotype was predominant, found in 170 individuals (56.86%), while the CC and CG genotypes were present in 71 (23.75%) and 58 (19.40%) individuals, respectively, (Table 4).

Table 4

Genotype frequencies of P21 and P53 polymorphisms in the control group (n = 299)

Gene	Genotype	n	Frequency (%)
P21	AA	114	38.13%
P21	CA	93	31.10%
P21	CC	92	30.77%
P53	GG	170	56.86%
P53	CC	71	23.75%
P53	CG	58	19.40%

4.3 DISTRIBUTION OF GENOTYPES AND THE ASSOCIATION OF THE *P21* (RS1801270) AND *P53* (RS1042522) POLYMORPHISMS WITH HPV INFECTION AND THE DEVELOPMENT OF CERVICAL LESIONS

The distribution of genotypes and the association of the *P21* (rs1801270) and *P53* (rs1042522) polymorphisms with HPV infection and the development of cervical lesions were analyzed, including odds ratios (OR), 95% confidence intervals (CI), and p-values.

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For the *P21* gene (rs1801270), individuals with the CA genotype showed an odds ratio (OR) of 2.23 (95% CI: 1.366–3.650; $p < 0.0001$) for HPV infection, while those with the AA genotype had an OR of 3.87 (95% CI: 2.455–6.113; $p < 0.0001$), compared to the CC genotype. For cervical lesions, the OR for the CA genotype was 1.28 (95% CI: 0.555–2.938; $p < 0.0001$) and for the AA genotype 1.39 (95% CI: 0.651–2.986; $p < 0.0001$), in comparison to the CC genotype.

For the *P53* gene (rs1042522), the GC genotype was associated with an OR of 2.45 (95% CI: 1.632–3.682; $p < 0.0001$), and the CC genotype with an OR of 1.74 (95% CI: 1.168–2.597; $p < 0.0001$), relative to the GG genotype, for HPV infection. Regarding cervical lesions, the CC genotype presented an OR of 0.049 (95% CI: 0.023–0.103; $p < 0.0001$), and the GC genotype an OR of 0.812 (95% CI: 0.366–1.806; $p < 0.0001$), both compared to the GG genotype, (Table 5).

Table 5

Genotypic distribution and association of P21 (rs1801270) and P53 (rs1042522) polymorphisms with HPV infection and cervical lesions, including low-grade squamous intraepithelial lesions (LSIL) and high-grade squamous intraepithelial lesions (HSIL)

SNP	Genotype	HPV+	HPV-	OR (95% CI)	p	HSIL	LSIL	OR (95% CI) / p
P21	CC	35	92	Ref.		22	13	
	CA	79	93	2.23 (1.366- 3.650)*	<0.0001	54	25	1.28 (0.555–2.938)* / <0.0001
	AA	168	114	3.87 (2.455–6.113)*	<0.0001	118	50	1.39 (0.651–2.986)* / <0.0001
P53	GG	110	170	Ref.		96	14	
	GC	92	58	2.45 (1.632–3.682)*	<0.0001	78	14	0.812 (0.366–1.806)* / <0.0001
	CC	80	71	1.74 (1.168–2.597)*	<0.0001	20	60	0.049 (0.023–0.103)* / <0.0001

Legend: HPV+, patients positive for human papillomavirus; HPV–, patients negative for human papillomavirus; OR, odds ratio; CI, confidence interval; LSIL, low-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion; Ref., reference genotype; $p < 0.0001$ indicates statistical significance.

Combined genotype analysis revealed significant associations between the *P21* (rs1801270) and *P53* (rs1042522) polymorphisms and susceptibility to cervical lesions. Among the 282 cases, the most frequent combined genotype was *P21* CA + AA / p53 GC + CC, observed in 152 individuals (53.90%), compared to 83 individuals (27.76%) among the 299 controls, serving as the reference group. Individuals carrying the *P21* CA + AA / *P53* GG genotype combination accounted for 33.69% of cases and 41.47% of controls, with an odds ratio (OR) of 0.42 (95% CI: 0.287–0.611; p < 0.0001).

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Those with the *P21* CC / *P53* GC + CC genotype represented 7.09% of cases versus 15.38% of controls, with an OR of 0.24 (95% CI: 0.132–0.428; p < 0.0001). The *P21* CC / *P53* GG genotype combination was found in 5.32% of cases and 15.38% of controls, showing the strongest inverse association with disease, with an OR of 0.18 (95% CI: 0.094–0.338; p < 0.0001), **(Table 6)**.

Table 6

Combined genotype frequencies of p21 (rs1801270) and p53 (rs1042522) polymorphisms in cases and controls, and their association with cervical lesion risk

Genotypes (*P21*)	Genotypes (*P53*)	Cases (n=282) n	Cases (n=282) %	Controls (n=299) n	Controls (n=299) %	OR (95% CI)
CA + AA	GC + CC	152	53.90	83	27.76	Ref.
CA + AA	GG	95	33.69	124	41.47	0.42 (0.287–0.611)*
CC	GC + CC	20	7.09	46	15.38	0.24 (0.132–0.428)*
CC	GG	15	5.32	46	15.38	0.18 (0.094–0.338)*

Legend: CA + AA, combined variant genotypes of *P21*; GC + CC, combined variant genotypes of *P53*; OR, odds ratio; CI, confidence interval; *p* < 0.0001 indicates statistically significant association. Cases: patients with cervical lesions (n = 282); Controls: HPV-negative women without lesions (n = 299). The reference group is CA + AA (p21) / GC + CC (*P53*).

4.4 DISTRIBUTION OF *P21* (RS1801270) AND *P53* (RS1042522) GENOTYPES TO ETHNICITY AND AGE

The distribution of *P21* (rs1801270) and *P53* (rs1042522) genotypes was also evaluated according to ethnicity and age, based on data collected from all patients. Specifically, in the experimental group comprising 282 individuals with cervical lesions, genotype frequencies were analyzed in relation to self-reported ethnicity (white or black) and age group (<50 years or ≥50 years).

Among white patients (n = 169), 24 (14.20%) carried the CC genotype and 145 (85.80%) had the combined CA + AA genotypes. Among black patients (n = 113), 11 (9.73%) had the CC genotype and 102 (90.27%) had CA + AA. No statistically significant association was observed between ethnicity and genotype distribution (OR = 0.652; 95% CI: 0.306–1.389; *p* = 0.265). Regarding age, among patients under 50 years (n = 176), 25 (14.20%) had the CC genotype and 151 (85.80%) had CA + AA. In those aged 50 years or older (n = 106), 10 (9.43%) had the CC genotype and 96 (90.57%) had CA + AA (OR = 0.629; 95% CI: 0.289–1.368; *p* = 0.239).

For the *P53* (rs1042522) polymorphism, among white patients, 61 (36.09%) had the GG genotype and 108 (63.91%) had the combined GC + CC genotypes. Among black

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patients, 49 (43.36%) had GG and 64 (56.64%) had GC + CC (OR = 1.356; 95% CI: 0.833–2.206; p = 0.220). Regarding age, 63 of the patients under 50 years (35.80%) carried the GG genotype and 113 (64.20%) carried GC + CC. Among those aged 50 or older, 47 (44.34%) had the GG genotype and 59 (55.66%) had GC + CC (OR = 1.429; 95% CI: 0.874–2.336; p = 0.154), (Table 6).

Table 6

Distribution of P21 (rs1801270) and P53 (rs1042522) genotypes by ethnicity and age among patients with cervical lesions (n = 282)

			P21			
		n = 282	**CC (n = 35)**	**CA + AA (n = 247)**	**OR (95% CI)**	**p**
Ethnicity	White	169	24	145	0.652 (0.306–1.389)	0.265
	Black	113	11	102		
Age	<50	176	25	151	0.629 (0.289–1.368)	0.239
	≥50	106	10	96		
			P53			
		n = 282	**GG (n = 110)**	**GC + CC (n = 172)**	**OR (95% CI)**	**p**
Ethnicity	White	169	61	108	1.356 (0.833–2.206)	0.220
	Black	113	49	64		
Age	<50	176	63	113	1.429 (0.874–2.336)	0.154
	≥50	106	47	59		

Legend: Genotype frequencies of p21 and p53 polymorphisms were evaluated according to self-reported ethnicity (white or black) and age group (<50 years or ≥50 years) in the experimental group. OR, odds ratio; CI, confidence interval; $p < 0.05$ was considered statistically significant. Genotypes were grouped as CC vs. CA + AA for p21, and GG vs. GC + CC for p53.

5 DISCUSSIONS

The present study, conducted in a population from Pernambuco, Brazil, identified a significant association between the polymorphisms *P21* (rs1801270) and *TP53* (rs1042522) and the risk of persistent HPV infection, Cervical Intraepithelial Neoplasia (CIN), and Uterine Cervical Cancer (UCC). The analysis revealed that genetic variations in cell cycle regulatory genes may modulate individual susceptibility to HPV driven cancer, contributing to the heterogeneity in clinical outcomes among infected women.

For the *P21* gene (rs1801270), carriers of the CA and AA genotypes exhibited a significantly higher risk of persistent HPV infection and progression to CIN - UCC, with the AA genotype showing the strongest effect (OR = 3.87; 95% CI: 2.455–6.113; p < 0.0001). This association supports a dose dependent influence of the A allele on disease susceptibility. Although no significant correlation was found between isolated genotypes and High-grade Squamous Intraepithelial Lesions (HSIL), the combined CA + AA genotypes were associated with a nearly threefold increase in CIN and cancer risk (OR =

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3.14; p = 7.57 × 10^{-8}), suggesting a cumulative effect of the variant allele on lesion progression.

These findings are in line with previous reports by Harima et al (2001) and Gbadegesin et al (2021), who demonstrated that the A allele may compromise p21 encoded protein function in cell cycle arrest, favoring genomic instability and impaired response to DNA damage. Functional analyses suggest that the rs1801270 variant alters the *CDKN1A* transcriptional response to *P53* activation, undermining the tumor suppressor pathway's ability to halt proliferation upon genotoxic stress (LI et al. 2011).

Conversely, studies in Asian populations have reported divergent results regarding the association between *p21* Ser31Arg and cervical cancer. WANG et al (2012) observed a protective effect of the A allele and AGT haplotype in a Chinese cohort, while LI-YA et al (2011) found no significant association in a large meta-analysis. These inconsistencies may stem from ethnic differences in allele distribution, environmental exposures, and methodological variations such as detection techniques and population stratification. Such contradictory findings underscore the importance of conducting population-specific studies and stratified meta-analyses to clarify these associations (BIRGANDER et al. 1996; WU et al. 2024).

With regard to the *TP53* gene (rs1042522), both the GC and CC genotypes were associated with increased risk of HPV infection compared to the GG genotype, consistent with previous literature from Gbadegesin et al (2021) and Zhao et al (2021). Notably, the CC genotype appeared to have a dual role: while contributing to HPV persistence (OR = 1.74; 95% CI: 1.168–2.597; p < 0.0001), it conferred a significant protective effect against HSIL (OR = 0.049; 95% CI: 0.023–0.103; p < 0.0001).

This apparent paradox may reflect stage-specific roles of the p53 protein, where certain polymorphic variants modulate its transcriptional activity differently under persistent viral infection compared to tumor development, as previously suggested by studies highlighting the context- dependent effects of p53 function and the influence of inherited polymorphisms on tumor initiation and progression (VOUSDEN & PRIVES, 2009; KRUSE & Gu, 2009; LEVINE, 1993; WHIBLEY et al. 2009).

This dual role of p53 polymorphisms may reflect stage-specific molecular dynamics during HPV-associated cervical carcinogenesis. In early stages, certain variants might impair immune surveillance or reduce p53-mediated transcriptional responses, contributing to viral persistence. Conversely, in later stages, these same variants may promote cell cycle

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arrest in genomically unstable cells, thereby exerting a protective effect. This stage-dependent behavior is thought to result from several interconnected mechanisms, including altered DNA-binding affinity of p53 to target gene promoters (FISCHER; SAMMONS, 2024), differential regulation of downstream genes such as p21 and its interaction with the DREAM complex (ENGLAND, 2022), and context-specific modulation of p53 stability and function, even in the presence of HPV oncogenes (CLEMENTE-SOTO et al. 2019).

The C allele encodes a p53 variant with modified apoptotic potential and altered interaction with the E6 oncoprotein of high-risk HPV types. This functional shift may, depending on the cellular context, hinder the early clearance of infected cells or provide a selective advantage to premalignant cells by promoting survival under genotoxic stress (HIETANEN et al. 2000; NAKAMURA et al. 2019). In the present study, the combined GC + CC genotypes were associated with increased susceptibility to CIN and cervical cancer, while also influencing HSIL outcomes—highlighting the multifaceted and context-dependent nature of p53-mediated responses.

Although our results are largely corroborated by previous studies, some publications -such as Wu et al (2004) and Zhang et al (2025) - did not detect significant associations between *TP53* polymorphisms and cervical lesions. These inconsistencies again highlight the multifactorial nature of cervical carcinogenesis, in which polymorphisms may act synergistically with environmental, epigenetic, and viral co-factors such as early sexual debut, multiparity, and immunologic status (LEE et al. 2004).

Taken together, our findings confirm that *P21* and *TP53* variants play relevant roles in modulating individual susceptibility to persistent HPV infection and lesion progression. Several meta- analyses and molecular studies support that *P21* and *TP53* polymorphisms are associated with altered risk of cervical lesions in HPV-infected populations (LOEB et al. 2012; XIAO et al. 2024; LIU et al. 2019).

Identifying high-risk genotypic profiles could enhance prevention efforts, early detection, and guide therapeutic decisions, particularly for immunotherapy or targeted treatments that depend on these genes' pathways — as shown by the combined use of molecular markers (*HPV* DNA, *P21*, *P53*) for survival prediction (ZHOU et al. 2012; HRSTKA, 2009).

Despite strengths such as a large sample size and lesion-severity stratification, the retrospective design and limitations in clinical data (age, self-declared ethnicity) must be acknowledged. Nevertheless, to the best of our knowledge, this is the largest Brazilian cohort

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to investigate the association of *P21* and *TP53* polymorphisms with cervical cancer, providing valuable insights for Latin American populations and reinforcing the importance of genetics in disease progression.

6 CONCLUSIONS

This study provides robust evidence that the p21 (rs1801270) and p53 (rs1042522) polymorphisms are significantly associated with persistent HPV infection, cervical lesion development, and progression to uterine cervical cancer in a Brazilian population. With a sample of 581 women—one of the largest cohorts reported in Brazil—this research offers important contributions to the understanding of host genetic susceptibility in HPV-related carcinogenesis. The findings underscore the potential clinical utility of these polymorphisms as molecular markers for risk stratification, early intervention, and personalized therapeutic strategies. Although limited by incomplete epidemiological records inherent to the retrospective design, the results highlight the need for further studies across diverse populations to validate these associations and support the integration of molecular genetics into cervical cancer prevention and management.

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