GSTT1 and GSTM1 polymorphisms with human papillomavirus infection in women from southern Brazil: a case–control study

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Abstract

Background  Important risk factors for the most common sexually transmitted infection (STI) in the world, human papillomavirus (HPV), include early sexual activity, use of contraceptives, tobacco smoking, and immunological and genetic factors. This study aimed to investigate the relationship between GSTM1 and GSTT1 polymorphisms and HPV infection and associated risk factors in a group of women assisted in the public health system of southwestern Paraná, Brazil.

Methods and results  A case–control study was designed with 21 women with HPV matched by age in the case group and 84 women without the virus in the control group. Viral detection was conducted via polymerase chain reaction (PCR) and GSTM1 and GSTT1 genotyping by Multiplex PCR. The results showed that the GSTT1 null allele was a protective factor against infection (ORadj 0.219; 95% CI 0.078–0.618; p = 0.004). No relationship was observed for the GSTM1 gene. Smoking was defined as a risk factor (ORadj 3.678; 95% CI 1.111–12.171; p = 0.033), increasing the chances of HPV by up to 3.6 times.

Conclusion  This study showed, for the first time, the relationship between GSTM1 and GSTT1 genetic polymorphisms and HPV. We found that this relationship protected women from southern Brazil from viral infection, but not from susceptibility.

Keywords  Human papillomavirus · Genetic polymorphism · Glutathione S-transferase · GSTM1 · GSTT1 · Tobacco

Introduction

The human papillomavirus (HPV) is a virus that can infect the skin and mucous membranes. It comprises about 220 distinct subtypes [1], out of which 40 can infect the anogenital tract, characterizing HPV as the most common sexually transmitted infection (STI) in the world [2]. Among the subtypes, 12 are defined as high risk for the development of cancer, including cervical cancer (CC), especially HPV-16 and HPV-18 [3]. In women, this type of cancer is the fourth most frequently diagnosed and the fourth leading cause of cancer death, with a global estimate of 604,000 new cases and 342,000 deaths in 2020 [4]. Although HPV infection is the main risk factor for CC, it is mostly an insufficient event if occurred alone [5].

Several factors significant in viral biology and disease progression are well defined in the literature, including ethnicity [6], early onset of sexual activity [7], use of contraceptives [8], exposure to tobacco [6, 9], co-infection with more than one viral subtype [10], oxidative stress [11], and immunological and genetic factors [12].
The cytosolic glutathione S-transferases (GSTs) belong to a family of enzymes involved in phase II of xenobiotic metabolism, being divided into eight gene classes: alpha (α), mu (μ), pi (π), theta (θ), sigma (σ), kappa (κ), omega (ω), and zeta (ζ) [13]. The GSTM1 and GSTT1 genes located on chromosome 1p13.3 and 22q11.23 exhibit insertion and deletion polymorphism, respectively, whereas the null allele characterizes the absence of enzymatic function [14]. This condition has been related to oxidative stress, which could be associated with pathologies including diabetes mellitus, prostate cancer [15], breast cancer [16], and CC [17]. It also favors the replication of pathogens, such as the human immunodeficiency virus (HIV), in different ethnic groups [18].

Despite gaps in the literature, evidence shows that genes involved in xenobiotic metabolism can affect the natural history of HPV subtypes, especially of those with high oncogenic risk [17]. Several studies indicate a relationship between GSTM1 and GSTT1 null genotypes and CC [19], but such relationship differs among populations and cannot be generalized [20]. An Indian study found a higher frequency of GSTM1 and GSTT1 null alleles in women with CC infected with the virus [21]. However, most studies prioritize the relationship between deleted alleles and viral infection events, not susceptibility [17, 22]. Sudenga et al. [17] found that HPV-16 infection was associated with null GSTM1 and GSTT1 genotypes, whereas deleted GSTM1 was associated with a lower persistence (or higher clearance) of the high-risk subtype.

A recent systematic review conducted by the authors of this research gathered studies that indirectly addressed the relationship between SNPs (single nucleotide polymorphisms), GSTM1 and GSTT1, and high-risk HPV infection in women with or without cervical alterations [23]. The study was inconclusive, but indicated a higher frequency of the GSTT1 null allele than of the deleted GSTM1 in women infected with high-risk HPV subtypes. Considering that no studies have been conducted on the direct relationship between SNPs and viral infection, an inconsistent subject, this study aimed to investigate the relationship between GSTM1 and GSTT1 polymorphisms and HPV infection and associated risk factors in a group of women assisted by the public health system in southwestern Paraná, Brazil.

Materials and methods

Study population and sampling

In 2017, 31,435 women aged 14–79 years were living in Francisco Beltrão. This number was used to estimate the study sample and determine the prevalence of cervical changes [Treco et al., 2021], exploring the prevalence of HPV infection in women under gynecological treatment in primary care units (UBS). The UBS included in the study were the family health strategy (FHS) units Antônio de Paiva Cantelmo, Cristo Rei, Industrial, and Pinheirinho. The Women’s Institute (Instituto da Mulher—IM), a reference center in outpatient gynecology and obstetrics care, was also included. Sample size was estimated with Epi Info version 7.2.2.6 (https://www.cdc.gov/epiinfo/support/por/pt_downloads.html), assuming a 25–30% prevalence of HPV infection. The power was set at 95%. The minimum sample size was 320 women and 10% more participants were added to avoid complications from losses and refusals, totaling 350 participants. All participants met the inclusion criteria of having had their first sexual intercourse at the time of the research, and pregnant women were excluded. Out of the 350 participants, 22 were diagnosed with HPV. Then, a case–control study was conducted with 105 women. Cases included women with HPV infection (n = 21; one participant was excluded since her genetic material did not allow characterizing genetic polymorphisms) whereas controls were formed by women without viral infection (n = 84). Cases and controls were matched by age (± 2 years), with four controls for each case.

Besides GSTM1 and GSTT1 polymorphism, other potential factors associated with HPV infection were assessed, including tobacco smoking, alcohol consumption, use of contraceptives, and vaginal infection, all with potential xenobiotic characteristics. Race was considered as a relevant variable for the investigated polymorphisms. All information on these variables were obtained by interviews conducted individually with a validated questionnaire [24].

During the gynecological consultation, women underwent material collection for the Pap smear. The endocervical brush used in the collection was placed in a microtube with 2 ml of saline solution kept at −20 °C until virus detection [24]. The storage of biological material and extraction of genetic material, viral detection, and GST polymorphisms were conducted at the Molecular Biology Laboratory of the Universidade Estadual do Oeste do Paraná, in Francisco Beltrão.

The project was approved by the Research Ethics Committee involving Human Beings (REC) and the National Research Ethics Committee (CONEP), Opinion No. 2.254.450 and CAAE: 72983817.5.0000.0107. After receiving information about the research, the women who agreed to participate signed the Informed Consent Form (ICF) (Appendix I) to be included in the study.

Total DNA extraction and HPV detection

A 200 µl aliquot of the original sample was used to isolate the total genetic material following the extraction and purification protocol “Biological Fluid/Blood Genomic DNA
“Purelink® Genomic DNA Mini Kit” (Invitrogen by Thermo Fisher Scientific, Carlsbad, California) according to the manufacturer’s instructions and stored in a freezer at −20 °C. For the molecular detection of HPV, specific primers were used for in vitro synthesis of the coding region of the virus’ L1 gene, MY09 (5’-CGTCMAAR GGAWACTGATC-3’) and MY11 (5’-GCMAAGGWCAT AAYAATGG-3’), producing a fragment of 450 bp. The final volume of each PCR reaction was 25 µl, with 10 mM Tris–HCl, 2 mM MgCl2, 0.1 mM dNTPs, 0.5 µM of each primer, 1.25 U of Taq DNA Polymerase (Ludwig Biotecnologia Taq DNA Polimerase, Brazil), and 3.5 µl of total DNA added at the end (50 ng/µl). To control the extraction and synthesis process, PCR of a 268 bp segment of the human β-globin gene was performed in all samples, using primers GH20 (5’-GAA GAG CCA AGG ACA GGT AC-3’) and PCO4 (5’-CAA CTT CAT CCA CGT TCA CC-3’). The amplifications of both genomes were processed in the thermocycler Applied Biosystems Veriti Thermal Cycler (Thermo Fisher Scientific, Germany) in this sequence: 10 min at 94 °C, followed by 37 cycles at 94 °C for 1 min, 55 °C for 1 min, 72 °C for 1 min, and finally, extension for 10 min at 72 °C. As a positive control for viral detection, a DNA sample from HeLa cells (HPV-16) was included. All amplicons were fractionated via 2% agarose gel electrophoresis, stained with ethidium bromide, visualized under ultraviolet light (UV), and photodocumented.

GSTM1 and GSTT1 genotyping

Genotyping was performed by Multiplex PCR. The primer pairs used were 5’-GAACCCCTGAAAGCCTAAGC-3’ (forward) and 5’-GGGGGCCGATACATA CGGGG-3’ (reverse) for GSTM1 and 5’-GAGCTGTCACACATCTC-3’ (forward) and 5’-TCACGGATCATGGCCAG CA-3’ (reverse) for GSTT1. The first pair produces an amplicon of 219 bp and the second of 459 bp. PCR conditions included initial denaturation at 94 °C for 5 min, followed by 35 cycles at 94 °C for 1 min, 58 °C for 1 min, 72 °C for 1 min, and 72 °C for 10 min. The genotypes were fractionated via 2% agarose gel electrophoresis, stained with ethidium bromide, visualized, and photodocumented. The presence of amplicons characterizes the functional alleles and the absence of null alleles.

Statistical analysis

Genotypic frequencies, GSTM1 and GSTT1, and the variables tobacco smoking, alcohol consumption, use of contraceptives, vaginal infection, and race were determined and compared between cases and controls using the chi-squared test ($\chi^2$), with Yates’ and Fisher’s correction for continuity. Variables with a significance value smaller than 0.20 were used for multivariate logistic regression, with a 95% confidence interval and $p < 0.05$, to determine the risk factors for STIs. All statistical analyzes were performed using the Statistical Package for the Social Sciences (SPSS) software version 24.0.

Results

Figure 1 shows the genotypic pattern of GSTM1 and GSTT1 genes and Table 1 shows the allele frequency spectrum. The GSTM1 null allele (GSTM1−) was more frequent in both cases (57.1%) and controls (75.0%). On the other hand, the GSTT1 null allele (GSTT1−) was less frequent (38.1%) in the case group than the GSTT1+ allele (61.9%) and more frequent in the control group (73.8%). Furthermore, the most common allelic combination was GSTM1−/GSTT1+ in the case group and double deletion in the control group.

Table 2 shows the results of the bivariate analysis (chi-squared test, $\chi^2$), suggesting associations between GST polymorphisms, life habits, vaginal infection, and race among individuals.
groups. The choice of variables was based on the possible relationship with xenobiotic metabolism, which is directly associated with GST genes. All categories established for GST polymorphism (GSTM1, p = 0.177; GSTT1, p = 0.004; Combinations, p = 0.002) and smoking (p = 0.040), recent vaginal infection (p = 0.132), and race (p = 0.043) categories suggested associations with HPV.

Although the use of contraceptives and the consumption of alcohol showed no significant association with the virus, 81% of women with HPV use or have used the medication and 61.9% consume some type of alcoholic beverage (Table 2).

Table 3 shows the variables that remained in the multivariate analysis and defined an explanatory model for viral infection. The GSTT1 null allele was defined as a protective factor (ORadj 0.219; 95% CI 0.078–0.618; p < 0.004), that is, women who have GSTT1 deletion are less susceptible to HPV infection than women in the control group. On the other hand, smoking was recognized as a risk factor, increasing the chance of viral infection up to 3.6 times

Table 1 Distribution of GST genotypes among the cases and controls of a group of women from the Municipality of Francisco Beltrão, Paraná

| Polymorphism          | Cases (n = 21) | Controls (n = 84) | Total (n = 105) |
|-----------------------|---------------|------------------|-----------------|
| GSTM1                 |               |                  |                 |
| Null/GSTM1−           | 12 (57.1%)    | 63 (75.0%)       | 75 (71.43%)     |
| Present/GSTM1+        | 9 (42.9%)     | 21 (25.0%)       | 30 (28.57%)     |
| GSTT1                 |               |                  |                 |
| Null/GSTT1−           | 8 (38.1%)     | 62 (73.8%)       | 70 (66.7%)      |
| Present/GSTT1+        | 13 (61.9%)    | 22 (26.2%)       | 35 (33.3%)      |
| Combinations          |               |                  |                 |
| GSTM1+/GSTT1+         | 6 (28.6%)     | 15 (17.9%)       | 21 (20%)        |
| GSTM1+/GSTT1−         | 3 (14.3%)     | 7 (8.3%)         | 10 (9.53%)      |
| GSTM1−/GSTT1+         | 7 (33.3%)     | 7 (8.3%)         | 14 (13.33%)     |
| GSTM1−/GSTT1−         | 5 (23.8%)     | 55 (65%)         | 60 (57.14%)     |

Table 2 Genetic polymorphism, life habits, vaginal infection, and race associated with HPV in a group of women from the Municipality of Francisco Beltrão, Paraná

| Variables               | Cases (n = 21) | Controls (n = 84) | Total | p-value |
|-------------------------|----------------|-------------------|-------|---------|
| GSTM1                   |               |                   |       |         |
| Null/GSTM1−             | 12 (57.1%)    | 63 (75.0%)        | 75 (71.4%) | 0.177b |
| Present/GSTM1+          | 9 (42.9%)     | 21 (25.0%)        | 30 (28.6%) |         |
| GSTT1                   |               |                   |       |         |
| Null/GSTT1−             | 8 (38.1%)     | 62 (73.8%)        | 70 (66.7%) | 0.004b |
| Present/GSTT1+          | 13 (61.9%)    | 22 (26.2%)        | 35 (33.3%) |         |
| Combinations            |               |                   |       |         |
| GSTM1+/GSTT1+           | 6 (28.6%)     | 15 (17.9%)        | 21 (20%) | 0.002c |
| GSTM1+/GSTT1−           | 3 (14.3%)     | 7 (8.3%)          | 10 (9.5%) |         |
| GSTM1−/GSTT1+           | 7 (33.3%)     | 7 (8.3%)          | 14 (13.3%) |         |
| GSTM1−/GSTT1−           | 5 (23.8%)     | 55 (65%)          | 60 (57.1%) |         |
| Contraceptives          |               |                   |       |         |
| No/has never used       | 4 (19.0%)     | 17 (20.2%)        | 21 (20.0%) | 1.000c |
| Uses/has already used   | 17 (81.0%)    | 67 (79.8%)        | 84 (80.0%) |         |
| Smoking                 |               |                   |       |         |
| Never smoked            | 14 (66.7%)    | 74 (88.1%)        | 88 (83.8%) | 0.040b |
| Smoker/ex-smoker        | 7 (33.3%)     | 10 (11.9%)        | 17 (16.2%) |         |
| Alcohol consumption     |               |                   |       |         |
| No                      | 8 (38.1%)     | 42 (50.0%)        | 50 (47.6%) | 0.464b |
| Yes                     | 13 (61.9%)    | 42 (50.0%)        | 55 (52.4%) |         |
| Vaginal infection       |               |                   |       |         |
| No                      | 10 (47.6%)    | 55 (65.5%)        | 65 (61.9%) | 0.132a |
| Yes                     | 11 (52.4%)    | 29 (34.5%)        | 40 (38.1%) |         |
| Race                    |               |                   |       |         |
| White                   | 14 (66.7%)    | 72 (85.7%)        | 86 (81.9%) | 0.043b |
| Others                  | 7 (33.3%)     | 12 (14.3%)        | 19 (18.1%) |         |

^aPearson’s χ² test
^bχ² with Yates’s correction for continuity
^cFisher’s exact test. Associations followed for multivariate analysis with p < 0.20
Table 3 Predictive factors for HPV infection in a group of women from the Municipality of Francisco Beltrão, Paraná, based on multivariate logistic regression analysis

| Variables                          | OR_{adj} | 95% CI       | p-value |
|-----------------------------------|----------|--------------|---------|
| GSTM1 Null                        | 0.960    | (0.289–3.189) | 0.947   |
| Present                           | 1 (Reference) |            |         |
| GSTT1 Null                        | 0.219    | (0.078–0.618) | 0.004   |
| Present                           | 1 (Reference) |            |         |
| Smoking                           |          |              |         |
| Smoker/ex-smoker                  | 3.678    | (1.111–12.171) | 0.033   |
| Never smoked                      | 1 (Reference) |            |         |
| Recent vaginal infection          |          |              |         |
| Yes                               | 2.140    | (0.745–6.145) | 0.158   |
| No                                | 1 (Reference) |            |         |
| Race                              |          |              |         |
| Others                            | 1.825    | (0.537–6.208) | 0.335   |
| White                             | 1 (Reference) |            |         |

$OR_{adj}$ value obtained from the multivariate logistic regression with $p<0.05$ and $R^2_{Nagelkerke}=0.20$ or 20%

$(OR_{adj} 3.678; 95\% CI 1.111–12.171; p<0.033)$. No interaction was observed between variables.

Discussion

To the best of our knowledge, this study’s results have shown, for the first time, that the GSTT1 null allele was characterized as a protective factor against viral infection, that is, women with GSTT1 deletion are less susceptible to HPV infection than women in the control group. On the other hand, smoking was defined as a risk factor, increasing the chance of viral infection up to 3.6 times.

Overall, individuals with GSTM1 and GSTT1 null genotypes are mostly susceptible to damage caused by oxidative stress [27]. This characteristic limits the combination of metabolites during phase II of xenobiotic metabolism, increasing the damage caused by oxidative stress and facilitating infection and viral replication [17]. This genotypic profile could also affect the natural history of infection of HPV STI [13].

Various pathologies, including rheumatoid arthritis, age-related macular degeneration, prostate cancer, lung cancer, CC, and schizophrenia have reported GSTM1 and GSTT1 SNPs [28–30]. Moreover, a recent study suggests that patients with severe acute respiratory syndrome (SARS) caused by SARS-CoV-2 (COVID-19) and with GSTT1 null genotype had higher mortality than those with the active allele [31]. More than 90% of CC cases are associated with HPV and several studies suggest that the GST null allele is associated with cancer development; however, these data differ between populations [20]. Most studies therefore prioritize the relationship between the deleted allele with the general course of the disease and not with the susceptibility of infection [17, 22].

Several studies suggest that individuals with homozygous deletion of both genes have limited or insufficient production of enzymes, decreasing detoxification and increasing the malignant transformation of cells which promote carcinogenesis [32]. Cancers related to the presence of the virus are head and neck cancer [33] and CC [19].

This study found no relationship between GSTM1 polymorphism and viral infection. However, it showed for the first time that the deleted GSTT1 decreases chances of HPV infection, protecting women with the null genotype (GSTT1−). Research conducted in patients with HIV suggests that deletions in GSTM1 and GSTT1 genes can slow disease progression [18]. Iorio et al. [34] confirm that GSTT1− is a protective genetic marker for allergic rhinitis. Another study found that both the GSTT1 deleted allele and its combined form with the GSTM1 null are protective factors for schizophrenia and reduce the Chinese population’s susceptibility to it [29].

Chen and Nirunsukkiri [35] observed that HPV infection behaves differently according to GST genotypes. Other studies believe that the product of GSTT1 is protects the host’s DNA against mutations [36]. Foppoli et al. [37] reported that high-risk subtypes can modulate and counteract the effects of increased levels of ROS (reactive oxygen species) in infected cells, that is, viral oncoproteins allow infected cells to survive in a hostile oxidizing environment, preventing the oxidation of anti-apoptotic and detoxifying enzymes. The E6 and E7 genes modulate cellular microRNAs that regulate genes associated with antioxidant response, suppression of OS-induced apoptosis, and regulation of antioxidant enzymes and compounds [38].

The activity of several antioxidant proteins, including those from the catalase family, peroxiredoxins, quinone oxidoreductase 1, and superoxide dismutase (SOD), can be disrupted by viral infections [38]. Furthermore, the expression of oncoproteins is associated with high levels of detoxifying enzymes, such as GSTs and GSH, giving the host cell an escape system from oxidative damage and resisting programmed cell death [38].

Similarly, Lee et al. [22] found that the GSTT1 null allele was protective in women infected with high-risk HPV even with the development of CC. However, the authors did not assess its association with susceptibility to infection. A recent systematic review suggested a risk association between null GSTT1 and infection by high-risk HPV subtypes [23]. Several studies confirm that GSTM1 and GSTT1 null alleles likely affect the progression of several types of cancer, including CC [19, 28],
but this finding is still divergent. More studies on the association of polymorphisms with infection by HPV and other viral agents are essential to better understand results similar to ours.

Different than GST polymorphism, smoking was identified as a risk factor for viral infection. In this study, the risk of HPV infection in smokers and ex-smokers was 3.6 times higher than in those who had never smoked. A Finnish study revealed that female smokers had a 1.76-fold higher susceptibility to infection, especially of subtype HPV-16 [39]. Another study, conducted in Greece, showed that women who smoke are 1.7 times more likely to be infected [40]. Several studies indicate tobacco smoking as a risk factor for HPV in different populations [41]. Tobacco smoking affects the immune system and increases the risk of new virus infections and HPV persistence [42]. Simen-Kapeu et al. [42] reported that young female smokers have a limited production of antibodies to fight high-risk oncogenic subtypes. Bergqvist et al. had similar findings [39]. However, the influence of smoking in the initial phase of HPV infections is still indefinite regarding cervical carcinogenesis [43]. Tobacco metabolites present in uterine cervical mucus decrease the quantity and function of epithelial Langerhans cells. This creates a local immunosuppressive effect which makes the host unable to develop an effective immune response, maximizing the risk of viral and persistent infections, including HPV [44, 45]. Tobacco consumption can also increase the carcinogenic action of the virus by inhibiting INF-γ, TNF-α, and mutations in the p53 gene, preventing apoptosis of the infected cell, and favoring the progression to cervical lesions and cancer [46]. Furthermore, components of cigarettes, including benzopyrene, nicotine, and derivatives, damage the cervical epithelium, favoring viral infection [46].

This study found that smoking characterized the exposure to xenobiotics in women, being a predictive factor for the risk of viral infection. Tian et al. [32] suggested a relationship between GSTT1 deletion and the chance of cervical changes in smokers. However, this and other studies [19] found no interaction between GST polymorphisms and smoking in the investigated population. This study has limitations, including the small number of women with HPV, which interfered with the statistical power of the analyses. Expanding the sample and including other populations to validate the results presented could solve this limitation. However, the case–control study also had strengths and allowed us to conclude that tobacco smoking is an important risk factor for viral infection. Furthermore, this was the first study to effectively assess the relationship between GSTM1 and GSTT1 and HPV STI, showing that the GSTT1 null allele can protect women from infection.

Conclusion

This study was conducted in the Municipality of Francisco Beltrão, in the State of Paraná. Results were unprecedented and characterized the GSTT1 null allele as a protective factor against viral infection, showing that women who have GSTT1 deletion are less susceptible to HPV infection than women in the control group. Moreover, smoking was defined as a risk factor, increasing the chance for viral infection in up to 3.6 times. Finally, other studies could expand the sample, dividing the groups between GSTT1−/GSTT1+ genotypes and smokers and non-smokers to see if they are associated.

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Author contributions Conceptualization: APRB and LCL; Methodology: APRB, VKV, ICT, CRP, GWW, and LCL; Formal analysis and investigation: APRB, GWW, and LCL; Writing—original draft preparation: APRB and LCL; Writing—review and editing: APRB, VKV, and LCL; Resources: ICT and LCL; Supervision: APRB and LCL.

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Consent to publish All authors approved the version to be published and agree to be accountable for all aspects of the work in ensuring related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Declarations

Conflict of interest All authors declare that they have no conflict to interest.

Informed consent All authors informed consent.

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