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# Polymorphisms in biotransformation and DNA repair genes, and survival on head and neck squamous cell carcinoma

## Polimorfismos em genes de biotransformação e reparo de DNA, e sobrevivência em carcinoma de células escamosas de cabeça e pescoço

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## ABSTRACT

**Objective:** This study analyzed the association between xenobiotic metabolism and DNA repair gene polymorphisms and overall survival (OS) and disease-free survival (DFS) in patients diagnosed with HNSCC in a Brazilian population. **Methods:** Retrospective study included 91 patients with a confirmed diagnosis of HNSCC. A total of 7 genes were analyzed: XRCC1, HOGG1, CYP1A1, GSTM1, GSTT1, GSTP1 and NAT2. **Results:** Regarding OS, the largest mean differences were observed comparing GSTT1 rs71748309 null and GSTT1 rs71748309 non-null genotypes (p=0.050). In the gene-gene interaction analysis, the higher difference to OS was observed to the combined genotypes of the GSTM1 rs4025935 and GSTT1 rs71748309 (p=0.286). Regarding DFS, the largest mean differences were observed comparing GSTT1 rs71748309 null and GSTT1 rs71748309 non-null genotypes (p=0.060) and to the combined genotypes of the GSTM1 rs4025935 and GSTT1 rs71748309 (p=0.313). **Conclusion:** None of the polymorphisms evaluated in xenobiotic metabolism or DNA repair genes were significantly associated with HNSCC survival in our population. Confirmation of these results in larger studies is required.

**Keywords:** : Squamous cell carcinoma of head and neck; Survival; Polymorphism, Genetic; DNA; Gene.

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## RESUMO

**Objetivo:** Este estudo analisou a associação entre o metabolismo xenobiótico e os polimorfismos do gene de reparo do DNA, e a sobrevivência geral (SG) e a sobrevivência livre de doença (SLD) em pacientes com diagnóstico de CECP em uma população brasileira. **Métodos:** Estudo retrospectivo que incluiu 91 pacientes com diagnóstico confirmado de CECP. Um total de 7 genes foram analisados: XRCC1, HOGG1, CYP1A1, GSTM1, GSTT1, GSTP1 e NAT2. **Resultados:** Em relação ao OS, as maiores diferenças médias foram observadas comparando os genótipos GSTT1 rs71748309 nulo e GSTT1 rs71748309 não nulo (p=0,050). Na análise da interação gene-gene, a maior diferença para OS foi observada para os genótipos combinados de GSTM1 rs4025935 e GSTT1 rs71748309 (p=0,286). Em relação ao DFS, as maiores diferenças médias foram observadas comparando os genótipos GSTT1 rs71748309 nulo e GSTT1 rs71748309 não nulo (p=0,060) e os genótipos combinados do GSTM1 rs4025935 e GSTT1 rs71748309 (p=0,313). **Conclusão:** Nenhum dos polimorfismos avaliados no metabolismo xenobiótico ou genes de reparo de DNA foram significativamente associados com a sobrevivência do CECP em nossa população. É necessária a confirmação desses resultados em estudos maiores.

**Descritores:** Carcinoma espinocelular de cabeça e pescoço; Sobrevivência; Polimorfismo Genético; DNA; Gene.

## INTRODUCTION

Head and neck squamous cell carcinoma (HNSCC) is the sixth most incident cancer worldwide.[1] Despite recent advances in prevention, detection, and diagnosis, the 5-year overall survival rate for HNSCC patients is among the lowest among the major malignancies.[2] Several studies have analyzed the role of polymorphic variants in different survival outcomes in HNSCC. Polymorphisms in X-ray repair enzyme by cross-complementation (*XRCC1*) and human 8-oxoguanine glycosylase 1 (*HOGG1*) genes, involved in the DNA repair pathway, and polymorphisms in N-acetyltransferase 2 (*NAT2*), glutathione S-transferase (GSTs) and cytochrome P450 1A1 (*CYP1A1*) genes, which are related xenobiotic metabolism pathways, are some examples of genetic factors studied in relationship to HNSCC survival.[3-8] The results suggest that variability on patients survival can be explained, at least in part, by polymorphisms in genes encoding enzymes involved in these biological pathways.[2,9-13] However, studies investigating the influence of polymorphisms on DNA repair and xenobiotic metabolism genes on HNSCC survival are still scarce for populations of developing countries. Thus, the aim of this study was to evaluate the impact of polymorphisms in biotransformation and DNA repair genes on overall survival (OS) and disease-free survival (DFS) in patients diagnosed with this type of carcinoma in a highly mixed population of northeastern Brazil.

## METHODS

### Recruitment of volunteers

The volunteers were recruited at the High Complexity in Oncology Center of the Santa Casa of Itabuna (CACON) and the Oncology Clinic of Ilhéus (CLIONI) between 2008 and 2009. 91 individuals, being 80 males, with a diagnosis of squamous cell carcinoma confirmed by anatomopathological examination were enrolled. All individuals signed the consent form approved by the Institutional Ethics Committee of the State University of Santa Cruz - UESC (Protocol Number: 134/2007). From each volunteer, three milliliters of peripheral blood were obtained that was later used in the extraction of genomic DNA.[14]

### Genotype tests

### PCR-RFLP genotyping

Polymorphisms for the *XRCC1 rs25487* (*Arg399Gln*), *HOGG1 rs1052133* (*Ser326Cys*), *CYP1A1 rs1048943* and *GSTP1 rs1695* (*Ile105Val*) genes were analyzed using the polymerase chain reaction (PCR) followed by restriction fragment length polymorphism (RFLP). For the polymorphism of the *XRCC1* gene the PCR product was digested by the restriction enzyme *MspI*. For the polymorphism of the *HOGG1* gene the PCR product was digested by restriction enzyme *MboI*.[15] For the *MspI* polymorphism of the *CYP1A1* gene the PCR product was digested by restriction enzyme *MspI*, generating a single band of 343bp for the wild-type allele and two bands (one of 134bp and one of 209bp) for the mutant allele. For the *BsmaI* polymorphism of the *GSTP1* gene the PCR product was digested by the restriction enzyme *MboI*.[16]

### *NAT2* gene sequencing and determination of acetylation profiles

The polymorphisms of the *NAT2* gene were genotyped by automated sequencing. Fourteen single nucleotide polymorphisms (SNPs) were analyzed: *C190T, G191A, C282T, T341C, G363A, A411T, A434C, C481T, G499A, G590A, C759T, A803G*, *G857A* and *A845C*. The PCR product (1141 bp) was sequenced on ABI3500 equipment (Applied Biosystems, Foster City, CA, USA), with the same PCR *primers* and

additionally with two internal *primers* for total coverage of the fragment.[15] The presence of the wild-type allele (absence of *NAT2* polymorphisms) defined the rapid and intermediate phenotype and its absence, the slow phenotype.

### Detection of complete deletion polymorphism for *GSTM1* and *GSTT1* genes

The *GSTM1* and *GSTT1* genes were amplified in a multiplex PCR, using the β-globin gene as the internal control of the reaction. The *null* genotypes for *GSTM1 rs4025935* and *GSTT1 rs71748309* were identified by the absence of 215 and 480bp amplification products, respectively.[14]

### Gene-gene interaction analysis

Genotype-genotype and genotype-phenotype interactions of the analyzed genes were performed. These interactions were considered to genes that participate in complementary biological pathway. Because of the reduced sample size, the genotype-genotype and genotype-phenotype combinations were dichotomized. The index group (higher risk) was formed by the combination of genotypes and phenotypes potentially associated with the highest risk of death in our population and the reference group by the sum of all the others genotype classes for these markers. For instance, in the combination of the *GSTM1* and *GSTT1* genes, the index group consisted of the combined *GSTM1 rs4025935 null* and *GSTT1 rs71748309 non-null* genotypes, and the reference group was composed of the other genotype classes (*GSTM1 rs4025935 null* and *GSTT1 rs71748309 null*, *GSTM1 rs4025935 non-null* and *GSTT1 rs71748309 non-null*, *GSTM1 rs4025935 non-null* and *GSTT1 rs71748309 null*).

### Measures of survival

Medical records of the patients participating in the study were used. Information regarding the date of diagnosis of the disease, the first day of the first treatment performed the date of death from any cause and the date of tumor recurrence were obtained. OS was defined as the interval between the first day, of the first treatment performed, and the date of death from any cause. DFS was measured as the interval between the first day of the first treatment performed and date of death from any cause or the date of tumor recurrence. Some individuals were censored due to non-occurrence of events. Censorship included patients who were alive up to the date of the last clinical evaluation recorded on medical records or until December 31, 2014, in order to guarantee a minimum follow-up of 5 years for all patients enrolled in the study.

### Statistical analysis

OS and DFS probabilities were estimated using the Kaplan-Meier method. The log-rank test was applied to evaluate the statistical significance of the differences between the survival curves with the respective 95% confidence intervals, according to the variables analyzed. All analyzes were conducted in the statistical package SPSS version 23.0 (SPSS, Chicago, IL, USA).

## RESULTS

The study population consisted of 91 patients diagnosed with HNSCC. In the analyzed period, 65 patients were alive and 12 of them had tumor recurrence. Of the total population studied, the mean age was 59 years (range 30 to 88 years), 87.9% were males, 86.8% were self-declared non-whites, 94.5% declared themselves smokers, 74.7% were always alcoholics, 86.9% had low level of schooling, and 91.1% presented tumor in advanced stage. The distribution of the primary tumor site was oral cavity (24.1%), the oropharynx (34.1%), the hypopharynx (7.7%), and the larynx (34.1%). The mean follow-up time was 28.1 months (SD=25.8; range 1 to 95 months). The mean time between diagnosis and initiation of treatment was 3.1 months (SD=9.6 months). The percentage of general deaths was 28.5% and the recurrence rate was 43.9%. The OS overall mean was 64.1 months (95% CI: 54.4 months-73.8 months). The DFS overall mean was 63 months (95% CI: 53 months-73 months). The 5-year OS rate was 67.6% and the 5-year DFS rate was 66.6% (Table 1).

The mean OS and DFS times, according to the analyzed genotypes, are shown in Table 2. With regard to OS the most remarkable differences, although not significant ($p$=0.050), was observed comparing *GSTT1* genotypes, with *GSTT1 rs71748309 null* individuals presenting a mean OS of 33.3 months (95% CI: 13.4 months-53.2 months) while for *GSTT1 rs71748309 non-null* the mean OS was 66.7 months (95% CI: 56.7 months-76.7 months) (Figure 1A). Regarding DFS, the larger difference was observed for *GSTT1* genotypes, with *GSTT1 rs71748309 null* individuals presenting a mean DFS of 33.3 months (95% CI: 13.4 months-53.2 months), whereas in those with *GSTT1 rs71748309 non-null* the mean DFS was 65.5 months (95% CI: 55.2 months-75.9 months) (Figure 1B). Although considerable, the observed differences were not statistically significant ($p$=0.060).

The mean OS and DFS times, according to gene-gene interactions are shown in Table 3. To OS the higher observed difference, although not significant ($p$=0.286), was verified for the combination of *GSTM1* and *GSTT1* genotypes, with *GSTM1 rs4025935 null* and *GSTT1 rs71748309 non-null* individuals presenting a mean OS value of 57.2 months (IC 95 %: 47.1 months-67.2 months), while individuals with other genotypic combinations had a mean OS of 60.2 months (95% CI: 47.6 months-72.7 months) (Figure 1C). Regarding DFS, the most marked differences were for the combination of *GSTM1* and *GSTT1* genotypes, with *GSTM1 rs4025935 null* and *GSTT1 rs71748309 non-null* individuals presenting a mean DFS value of 51.7 months (IC 95 %: 42.5 months-60.8 months), while individuals with other genotypic combinations had a mean DFS of 59.5 months (95% CI: 46.8 months-72.3 months) (Figure 1D). Although considerable, again the observed differences were not statistically significant ($p$=0.313).

**Table 1.** Characteristics of patients diagnosed with HNSCC.

| Characteristics | N (%) |
|---|---|
| **Sex** | |
| Male | 80 (87.9%) |
| Female | 11 (12.1%) |
| Age, mean (SD) | 59 years (11.6%) |
| **Color skin** | |
| White | 12 (13.2%) |
| Non-white | 79 (86.8%) |
| **Smoker** | |
| Always | 86 (94.5%) |
| Never | 5 (5.5%) |
| **Alcoholic** | |
| Always | 68 (74.7%) |
| Never | 23 (25.3%) |
| **Education** | |
| Illiterate | 15 (16.5%) |
| Subscribe name only | 20 (22%) |
| Literate | 12 (13.2%) |
| Incomplete Elementary School | 29 (31.9%) |
| Complete Elementary School | 3 (3.3%) |
| Incomplete High School | 1 (1.1%) |
| Complete High School | 7 (7.6%) |
| Incomplete College | 2 (2.2%) |
| Complete College | 2 (2.2%) |
| **Stage of tumor**[a] | |
| I | 3 (3.8%) |
| II | 4 (5.1%) |
| III | 12 (15.2%) |
| IV | 60 (75.9%) |
| **Primary site of tumor** | |
| Oral cavity | 22 (24.1%) |
| Oropharynx | 31 (34.1%) |
| Hypopharynx | 7 (7.7%) |
| Larynx | 31 (34.1%) |
| Follow-up time, mean (SD) | 28.1 months (25.8) |
| Time between diagnosis and treatment, mean (SD) | 3.1 months (9.6) |
| General deaths | 26(28.5%) |
| Recurrence or death | 40(43.9%) |
| Overall survival, mean (95% CI) | 64.1 months (54.4-73.8) |
| Disease-free survival, mean (95% CI) | 63 months (53-73.8) |
| 5 year overall survival | 67.6% |
| 5 year disease-free survival | 66.6% |

[a] Some patients (n=12) did not have the specified data.

## DISCUSSION

In this study, we investigated the association of polymorphisms in biotransformation and DNA repair genes with the survival of patients diagnosed with HNSCC. Although no significant association was found in the present study, the impact of variants in these genes on HNSCC and other cancers survival was previously reported.[17-20]

Survival did not differ significantly for the *GSTM1 rs4025935 null* and *GSTM1 rs4025935 non-null* genotypes in 106 Chinese patients diagnosed with ovarian cancer and treated with chemotherapy. The *GSTP1 rs1695* (*Ile105Val*) *Ile/Val* (heterozygote) genotype showed no increased risk of death compared to the genotype *GSTP1 rs1695* (*Ile105Val*) *Ile/Ile* (wild homozygote).[19] In other studies was reported that polymorphism of the *GSTP1 rs1695*

**Table 2.** Mean times of overall and disease-free survival according to the genotypes of patients diagnosed with HNSCC.

| Genotypes and phenotypes | Mean overall survival (95% CI) (in months) | p value | Mean disease free survival (95% CI) (in months) | p value |
|---|---|---|---|---|
| GSTM1 rs4025935 null | 55.8(46.2-65.4) | 0.457 | 50.5(41.8-59.3) | 0.482 |
| GSTM1 rs4025935 non-null | 60.4(47.2-73.6) | | 59.7(46.2-73.1) | |
| GSTT1 rs71748309 null | 33.3(13.4-53.2) | 0.050 | 33.3(13.4-53.2) | 0.060 |
| GSTT1 rs71748309 non-null | 66.7(56.7-76.7) | | 65.5(55.2-75.9) | |
| GSTP1 rs1695 (Ile105Val) | 61.7(48.8-74.6) | 0.901 | 60.3(47.1-73.5) | 0.850 |
| Ile/Val or Val/Val | | | | |
| GSTP1 rs1695 (Ile105Val) | 64(50.3-77.7) | | 63.9(50.2-77.6) | |
| Ile/Ile | | | | |
| CYP1A1 rs1048943 TC or CC | 56.8(43.2-70.3) | 0.542 | 54.9(40.7-69.1) | 0.511 |
| CYP1A1 rs1048943 TT | 66.3(53.8-78.7) | | 65.7(53.1-78.3) | |
| XRCC1 rs25487 (Arg-399Gln) | 54.2(40.7-67.8) | 0.409 | 53.4(39.5-67.2) | 0.418 |
| AA or GA | | | | |
| XRCC1 rs25487 (Arg-399Gln) | 68.2(56.3-80.1) | | 66.6(53.8-79.4) | |
| GG | | | | |
| HOGG1 rs1052133 | 62.5(45.5-79.4) | 0.947 | 61.2(43.7-78.7) | 0.964 |
| (Ser326Cys) CG or GG | | | | |
| HOGG1 rs1052133 | 63.4(51.8-74.9) | | 62.3(50.4-74.1) | |
| (Ser326Cys) CC | | | | |
| NAT2 slow | 65.8(51.1-80.6) | 0.797 | 63.6(47.7-79.4) | 0.961 |
| NAT2 rapid or intermediate | 60.9(47.7-73.6) | | 59.9(46.5-73.2) | |

(*Ile105Val*) was positively associated with second primary malignancies in patients treated to HNSCC[21] and individuals with *GSTT1 rs71748309 non-null* genotype were more likely to die from HNSCC during the course of their disease.[22]

Silva et al. (2010),[17] in turn, reported that the *GSTT1 rs71748309 non-null* genotype presented an inverse relationship between the risk of developing brain tumors and the survival rate in patients with malignant gliomas. In that study, this variant was associated with protection against cancer development and at the same time it was related to a lower OS.[17] This same pattern was verified in our findings, since a higher OS rate was observed among the individuals with *GSTT1 rs71748309 non-null* genotype, which was a risk factor for HNSCC in a previous case-control study carried out in the same population of present study.[14]

In the present study, no significant association was observed between the polymorphisms *GSTM1 rs4025935 null* and *CYP1A1 rs1048943 MspI* and the OS of patients with HNSCC. A similar result was reported in a study conducted in the southeastern region of Brazil involving 153 patients diagnosed with HNSCC.[23]

Although in our population we have not observed any significant association of polymorphisms in *XRCC1 rs25487* (*Arg399Gln*) and *HOGG1 rs1052133* (*Ser326Cys*) repair genes with OS or DFS in HNSCC, the influence of these genes on survival rates in HNSCC and other cancers has been reported elsewhere. In a study conducted in a population of the United States, for example, a strong relationship has been demonstrated between the expression of the enzyme *XRCC1* and the OS of patients diagnosed with head and neck cancer. Elevated *XRCC1* enzyme expression was associated with lower survival, particularly in patients treated with chemotherapy.[11] Patients with lung cancer from a North Indian population with *XRCC1 rs25487* (*Arg399Gln*) AA (variant homozygote) genotype had an increase in OS compared to those with *XRCC1 rs25487* (*Arg399Gln*), GG (wild homozygote), and *XRCC1 rs25487* (*Arg399Gln*) GA (heterozygote) genotypes.[24]

Other studies enrolling large samples found that the variant allele A of *XRCC1 rs25487* (*Arg399Gln*) was

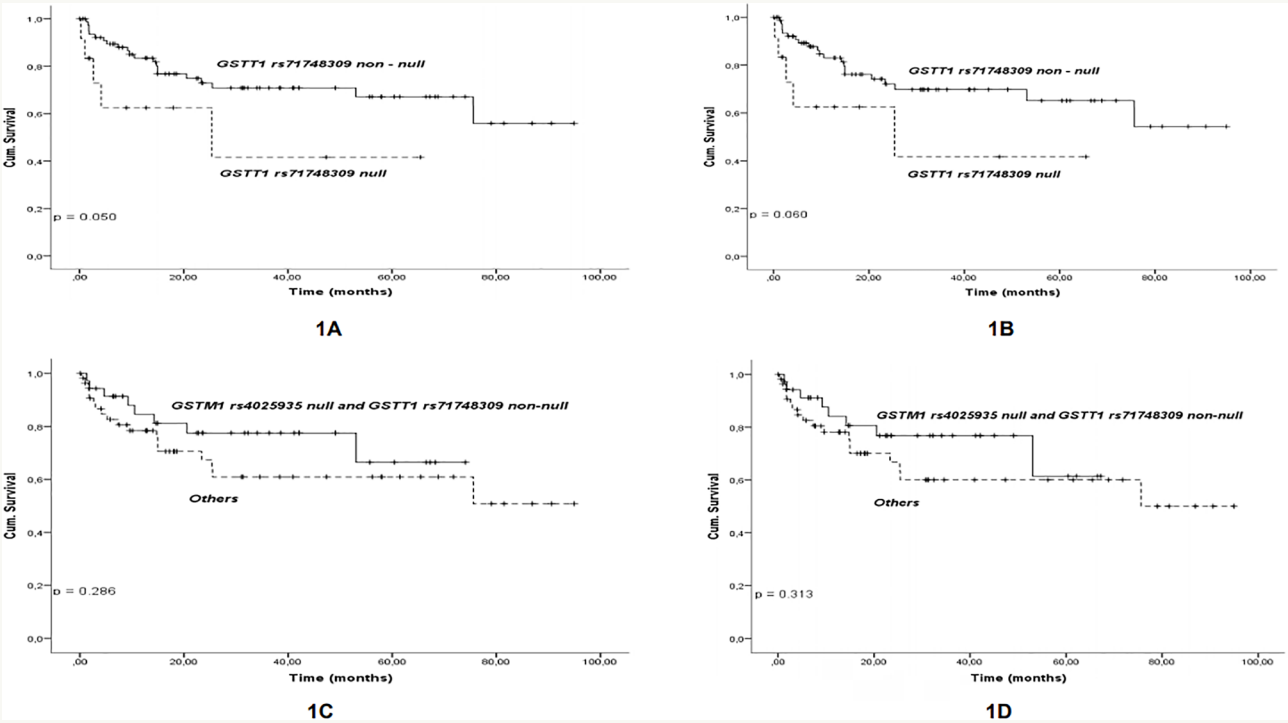


**Figure 1.** Overall survival and disease-free survival curves. A. With regard to OS, were observed among GSTT1 genotypes, with GSTT1 rs71748309 null individuals presenting a mean OS value of 33.3 months (95% CI: 13.4 months-53.2 months) while for those GSTT1 rs71748309 non-null the mean OS value was 66.7 months (95% CI: 56.7 months-76.7 months), p=0.050; B. GSTT1 genotypes, with GSTT1 rs71748309 null individuals presenting a mean DFS of 33.3 months (95% CI: 13.4 months-53.2 months), whereas in those with GSTT1 rs71748309 non-null the mean DFS was 65.5 months (95% CI: 55.2 months-75.9 months), p=0.060; C. Regarding OS, the higher observed difference, although not significant, was verified for the combination of GSTM1 and GSTT1 genotypes, with GSTM1 rs4025935 null and GSTT1 rs71748309 non-null individuals presenting a mean OS value of 57.2 months IC 95 %: 47.1 months-67.2 months), while individuals with other genotypic combinations had a mean OS of 60.2 months (95% CI: 47.6 months – 72.7 months), p=0.286; D. Regarding DFS, the most marked differences were for the combination of GSTM1 and GSTT1genotypes, with GSTM1 rs4025935 null and GSTT1 rs71748309 non-null individuals presenting a mean DFS value of 51.7 months (95% CI: 42.5 months-60.8 months), while individuals with other genotypic combinations had a mean DFS of 59.5 months (95% CI: 46.8 months-72.3 months), p=0.313. Although considerable, again the observed differences were not statistically significant.

**Table 3.** Mean times of overall and disease-free survival according to gene-gene interactions of patients diagnosed with HNSCC.

| Genotypes and phenotypes | Mean overall survival (95% CI) (in months) | p value | Mean disease free survival (95% CI) (in months) | p value |
|---|---|---|---|---|
| GSTM1 rs4025935 null and GSTT1 rs71748309 non-null | 57.2(47.1-67.2) | 0.286 | 51.7(42.5-60.8) | 0.313 |
| Other genotypic combinations | 60.2(47.6-72.7) | | 59.5(46.8-72.3) | |
| GSTM1 rs4025935 null and GSTP1 rs1695 (Ile105Val) Ile/Val or Val/Val | 57.7(46.4-69) | 0.374 | 52.4(42.2-62.7) | 0.395 |
| Other genotypic combinations | 60.9(49.2-72.6) | | 60.1(48.1-72) | |
| GSTT1 rs71748309 non-null and GSTP1 rs1695 (Ile105Val) Ile/Val or Val/Val | 64.6(51-78.2) | 0.539 | 63(48.9-77) | 0.601 |
| Other genotypic combinations | 60.8(48.1-73.5) | | 60.6(47.8-73.4) | |
| CYP1A1 rs1048943 TC or CC and NAT2 slow | 73.2(55.9-90.6) | 0.373 | 73.2(55.9-90.6) | 0.475 |
| Other genotypic/phenotypic combinations | 60.8(49.3-72.2) | | 59.8(48.2-71.5) | |
| XRCC1 rs25487 (Arg399Gln) AA or GA and HOGG1 rs1052133 (Ser326Cys) CG or GG | 41.9(25.3-58.5) | 0.806 | 39(20.8-57.2) | 0.678 |
| Other genotypic combinations | 64.7(54.6-74.8) | | 63.9(53.6-74.3) | |
| GSTM1 rs4025935 null and CYP1A1 rs1048943 TC or CC | 42.7(27.9-57.4) | 0.523 | 42.7(27.9-57.4) | 0.547 |
| Other genotypic combinations | 65.5(55.1-75.9) | | 64.7(54.1-75.3) | |
| GSTT1 rs71748309 non-null and CYP1A1 rs1048943 TC or CC | 59.9(45.4-74.3) | 0.911 | 57.7(42.3-73.1) | 0.963 |
| Other genotypic combinations | 63.3(51.1-75.5) | | 62.7(50.4-75.1) | |
| GSTP1 rs1695 (Ile105Val) Ile/Val or Val/Val and CYP1A1 rs1048943 TC or CC | 53.4(35.5-71.2) | 0.545 | 51(32.1-69.9) | 0.490 |
| Other genotypic combinations | 65.7(55.1-76.4) | | 65.1(54.3-75.9) | |

associated with improved OS or prolonged time to recurrence in patients with head and neck cancer. In contrast, a smaller study of 98 individuals genotyped for *XRCC1 rs25487* (*Arg399Gln*) found no association with outcome.[4] Costa et al. (2016),[25] reported that polymorphisms in *HOGG1 rs1052133* (*Ser326Cys*) were associated with shorter progression free disease in patients with advanced tumor stage of oropharyngeal squamous cell carcinoma.[25] In turn, Chinese patients diagnosed with lung cancer presenting *HOGG1 rs1052133* (*Ser326Cys*) CG (heterozygote) and *HOGG1 rs1052133* (*Ser326Cys*) *GG* (variant homozygote) genotypes showed a reduced OS compared to those with the *HOGG1 rs1052133* (*Ser326Cys*) *CC* (wild homozygote) genotype, especially in females.[12]

There are at least sixty known *NAT2* polymorphisms grouped into slow, intermediate and rapid acetylator phenotypes that have been previously associated with cancer risk in other studies.[18] In addition, the *NAT2* gene can be an important prognostic factor for the survival of patients in other types of cancers.[10] Previous analysis showed that *NAT2* rapid acetylator phenotypes had a 19.7% increased 5-year OS rate compared to *NAT2* slow acetylator in oropharyngeal and oral cavity cancer cases.[18]

## CONCLUSION

In the present study, some outstanding differences for OS and DFS according to analyzed genetic variants were observed, although they were not statistically significant. The small sample size is an important limitation, resulting in part of the difficulties of performing a follow-up of cancer patients residing in the interior of Brazil based on search to secondary data deposited in systems that were not originally developed for research purposes. The results obtained in the present study should be confirmed in the future in larger and better-designed studies, in addition to meta-analysis studies, in order to clarify the true role of these variants on survival in the HNSCC.

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