REVIEW ARTICLE

ASSOCIATION OF POLYMORPHISMS IN GASTRIC CANCER IN LATIN AMERICAN INDIVIDUALS: A BRIEF SYSTEMATIC REVIEW

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Highlights: (1) Genetic polymorphisms can serve as biomarkers for susceptibility to gastric cancer. (2) Polymorphisms in genes that potentiate the inflammatory response against *Helicobacter pylori* infection increase the risk of gastric cancer when associated with alcoholism and smoking. (3) Some polymorphisms are associated with therapeutic failure in patients in northern Brazil.

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ABSTRACT

Objective: To systematically compile all information that clarifies which genetic polymorphisms are associated with gastric cancer in South American individuals. **Methods:** A systematic review was conducted following the PRISMA model and PICO strategy, based on the guiding question: "Which genetic polymorphisms are related to gastric cancer in the Latin American population?" Articles were searched in the PubMed, LILACS, BVS, and Google Scholar databases, following defined inclusion and exclusion criteria. Fifty-two articles were found, and after analysis, 12 were definitively included in the review. **Results:** Several polymorphisms were identified in various genes involved in gene regulation, protein coding, inflammatory processes, oncological malnutrition, and drug-gene interaction, acting as potential molecular markers for the development of gastric cancer. **Conclusion:** The discovery of possible biomarkers that guide the relationship between gastric cancer and the polymorphisms of the genes studied in this review is promising. However, further studies are needed to better investigate this relationship and clarify the development of this pathology based on variations in various genes, allowing for future diagnostic approaches based on Single Nucleotide Polymorphism and genetic intervention in gastric cancer.

Keywords: Stomach Neoplasms, Gene Polymorphism, Latin American Peoples, Genetics

ASSOCIAÇÃO DE POLIMORFISMOS EM CÂNCER GÁSTRICO EM INDIVÍDUOS LATINO-AMERICANOS: UMA BREVE REVISÃO SISTEMÁTICA DA LITERATURA

RESUMO

Objetivo: Compilar sistematicamente todas as informações que esclareçam quais polimorfismos genéticos se associam ao câncer gástrico em indivíduos sul-americanos. **Métodos:** Foi realizada uma revisão sistemática seguindo o modelo PRISMA e a estratégia PICO, com base na pergunta norteadora: "Quais polimorfismos genéticos estão relacionados ao câncer gástrico na população latino-americana?" Os artigos foram pesquisados nos bancos de dados PubMed, LILACS, BVS e Google Scholar, seguindo os critérios de inclusão e exclusão definidos. Foram encontrados 52 artigos e, após análise, 12 foram definitivamente incluídos na revisão. **Resultados:** Foram identificados diversos polimorfismos em diversos genes envolvidos na regulação gênica, codificação de proteínas, processos inflamatórios, desnutrição oncológica e interação droga-gene, atuando como potenciais marcadores moleculares para o desenvolvimento do câncer gástrico. **Conclusão:** A descoberta de possíveis biomarcadores que orientam a relação entre o câncer gástrico e os polimorfismos dos genes estudados nesta revisão é promissora. No entanto, são necessários mais estudos para investigar melhor essa relação e esclarecer o desenvolvimento dessa patologia com base em variações em múltiplos genes, permitindo futuras abordagens de diagnóstico baseadas no polimorfismo de nucleotídeo único e na intervenção genética no câncer gástrico.

Palavras-chave: Neoplasias gástricas, polimorfismo genético, População Sul Americana, Genética

INTRODUCTION

Globally, the prevalence of gastric cancer (GC) or gastric adenocarcinoma ranks among the top 5 types of cancer worldwide. Its incidence is significant in the following regions: East Asia, Eastern Europe, and Latin America[2]. Currently, in Latin America, Brazil has the highest

prevalence of this pathology, with the Southeast, North, and Northeast regions showing the highest rates of GC[1,2,3].

Gastric cancer ranks as the 5th most incident cancer worldwide and the 3rd leading cause of cancer mortality, accounting for approximately 970,000 new cases and 660,000 deaths annually. In Brazil, the estimated incidence rate is 7.5 cases per 100,000 men and 3.8 cases per 100,000 women, with higher frequency among individuals over 60 years old. Mortality also shows a sex disparity, with rates of 6.1/100,000 in men and 2.9/100,000 in women, highlighting the male population as more vulnerable. Regionally, the North and Northeast present the highest incidence, while the South and Southeast have shown a decreasing trend, likely related to earlier diagnosis and improved healthcare access.

Although a large body of studies on genetic polymorphisms associated with gastric cancer is available in Asian and European populations, systematic investigations in Latin America remain scarce. This scientific gap limits the understanding of the role of genetic factors in gastric cancer development in populations characterized by high miscegenation and socio-environmental heterogeneity, such as Brazil. Therefore, expanding evidence in this region is essential to support screening, prevention, and treatment strategies tailored to the specificities of Latin American populations.

In the Brazilian population, factors such as racial mixing, socio-economic and demographic subjectivities across its five regions, along with the morbidity profiles of non-communicable chronic diseases and late diagnosis, contribute to the high prevalence and incidence rates of GC in Latin America[4].

That said, GC pathogenesis may also be influenced by an unfavorable microbiome, promoting the predominance of pathogenic bacteria over protective commensal species. The manifestation of GC is prevalent in regions that exhibit cultural habits related to the consumption of foods mainly processed through brining, curing, and industrial methods[5]. Dietary habits involving foods with chemical properties, preservatives, flavor enhancers, and colorants are essential contributors to the development of GC[5,6]. Additionally, the regional diet rich in chemical derivatives of Manihot esculenta Crantz (cassava) may also be a strong driver of GC occurrence in Amazonian populations[7]. On the other hand, lifestyle is linked to heterogeneity in populations with genetic ancestry that may predispose them to developing GC and other cancers[6.]

There are about 52 identified risk factors for GC, most of which are associated with advanced-stage pathology and late diagnosis[8]. Thus, carcinogenesis results from genetic and environmental factors that, when related, explain the epigenetic action leading to histological changes in the simple columnar mucosal epithelium of the stomach, resulting in carcinoma[9].

Furthermore, GC can manifest in individuals who are more predisposed and susceptible, such as those with pre-existing conditions like pernicious anemia, Epstein-Barr virus infection, and individuals with blood type A[8]. GC pathogenesis can also begin due to an unfavorable microbiome, which strengthens the proliferation of harmful bacteria in competition with protective ones[10]. Helicobacter pylori is an etiological agent that colonizes the gastric mucosa, and its pathogenicity can be favored by external environmental and dietary factors[11].

Therefore, the objective of this study is to systematically compile all available information from the main databases to clarify which genetic polymorphisms are associated with the risk of gastric cancer in Latin American individuals, in order to provide greater clarity on the molecular pathogenesis and guide evidence-based medicine for treatment and genetic intervention in this pathology.

METHODOLOGY

The present study is a systematic literature review based on the recommendations of the Preferred Reporting Items for *Systematic Reviews and Meta-Analyses* (PRISMA)[12], aiming to analyze the relationship between genetic polymorphisms and the development of gastric cancer in the Latin American population.

To this end, the study was guided by the following research question: "Which genetic polymorphisms are related to gastric cancer in the Latin American population?" based on the *Population, Intervention, Comparison, and Outcome* (PICO) strategy[13].

Using the *Descriptors in Health Sciences* (DeCS) and *Medical Subject Headings* (MeSH), the following descriptors were selected in Portuguese and English: “fatores nutricionais, fatores nutrigenéticos, fatores nutrigenômicos, nutritional factors, nutrigenetic factors, nutrigenomic factors,” which were combined with: gastric cancer, incidence, Latin America, Brazil, North Region, individually using the Boolean operators "AND" and "OR."

The articles for this review were searched between November 13, 2023, and December 10, 2023, without publication date restrictions, in the *U.S. National Library of Medicine* (NLM) – *PubMed, Latin American and Caribbean Health Sciences Literature* (LILACS), *Virtual Health Library* (VHL), and grey literature databases (Google Scholar).

The review included original and complete observational studies, freely available in English, Spanish, and Portuguese, that answered the guiding question. Excluded from the study were controlled clinical trials, duplicate articles, other reviews, articles unrelated to the topic, those that were not open access, and those that did not answer the guiding question.

The storage, reading, and screening of the articles were carried out using the *Mendeley platform* (Reference Management Software), and the organization was done using Google Docs. Five reviewers performed a thorough analysis according to inclusion and exclusion criteria, and the selected articles were equally divided among the reviewers. After applying the inclusion and exclusion criteria, the research steps included reading the article titles, reading the abstracts, and reading and evaluating the remaining studies from the previous stages in full.

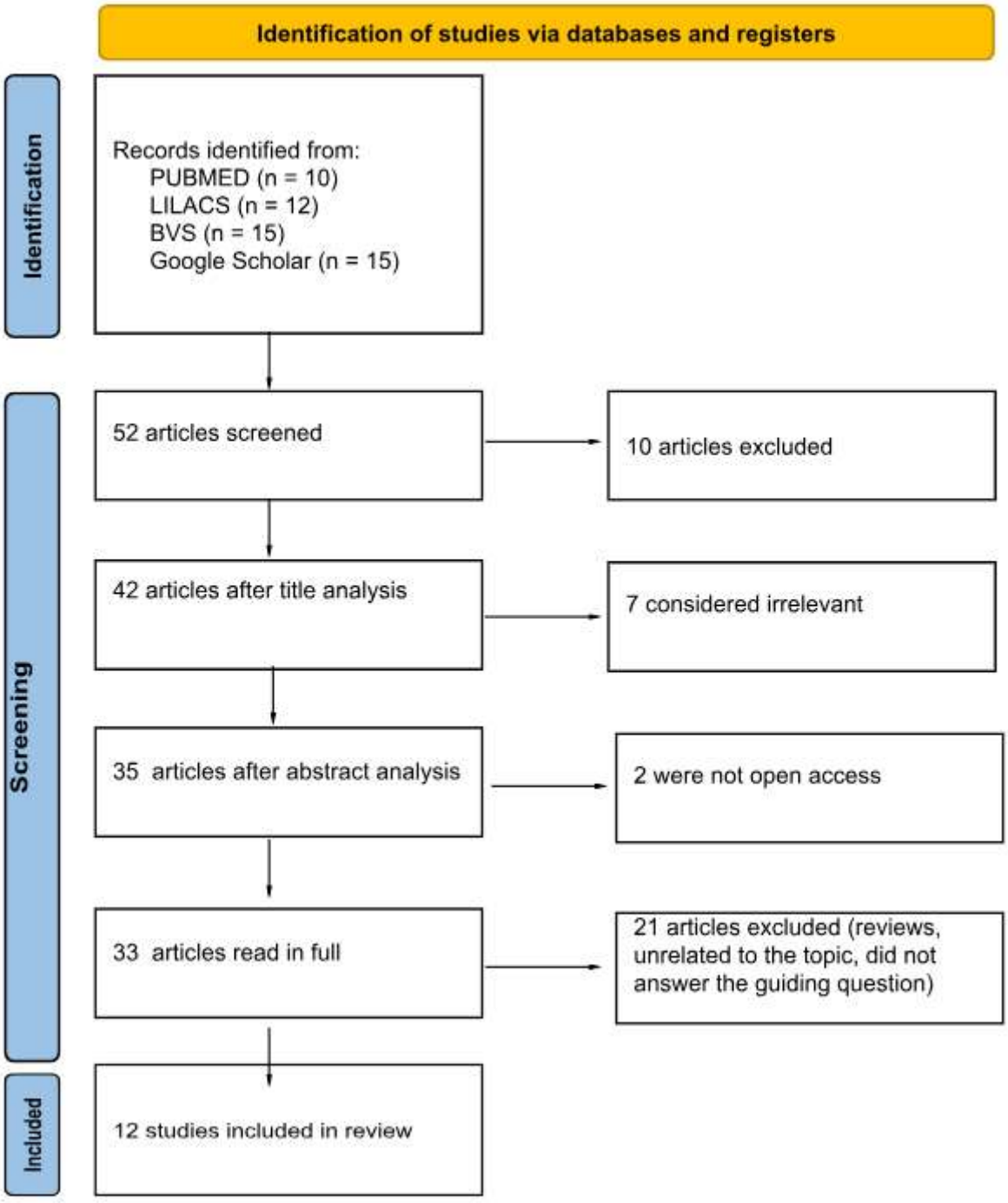
The prospective protocol for this systematic review was submitted to the OSF Registries platform under the number 10.17605/OSF.IO/T7AGF. The methodological quality of the cohort and case-control observational studies was assessed using the Joanna Briggs Institute (JBI)[14,15] tool and the Newcastle-Ottawa Scale (NOS)[16], while the cross-sectional study was assessed only by the JBI tool. The quality assessment process was conducted by two independent reviewers using a blinded analysis. The results of these preliminary analyses were subsequently compared and discussed among the reviewers to reach a final consensus on the methodological quality classification of each study.

RESULTS

A total of 52 articles were found in the databases, with 10 in PUBMED, 12 in LILACS, 15 in VHL, and 15 in Google Scholar. After applying the inclusion and exclusion criteria, 42 articles were selected.

In the analysis phase, after reading the titles, 35 were related to the topic and were deemed eligible for abstract reading. Finally, 33 articles remained for full-text reading, of which 12 were definitively included in this review. Figure 1 outlines the selection process, and Table 1 provides a summary of the key articles in this research.

Figure 1 - Flowchart of the articles selection process



Source: Os autores

Table 1 - Description of the articles definitively included in the review.

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Author/Year	Sample	Objective	Conclusion
Dantas RN, et al. 2019[17].	102 histopathological tissue samples from gastric adenocarcinoma, and 102 samples without gastric cancer (GC)	To evaluate the association of allele and genotypic frequencies of *PSCA* (rs2976392), *TNF-α* (rs1800629), *PARP1* (rs1136410) and *TP53* (rs368771578) SNPs with susceptibility to GC in a Brazilian population.	The *PSCA* (rs2976392) SNP has been associated with the risk of GC, and its presence may correspond to a possible molecular marker for the development of GC. *TNF-α* (rs1800629) was also associated with the risk of GC in the sample. On the other hand, *PARP1* (rs1136410) and *TP53* (rs368771578) were not associated.
Fu L, et al. 2023[18].	220 patients with GC	To evaluate the association between single nucleotide polymorphism (SNP) - 2028 A/G of the *SELP* gene and malnutrition in patients receiving chemotherapy for gastric cancer(GC).	Patients carrying the A allele had a reduced risk of developing malnutrition compared to patients with the GG genotype. In addition, the multivariate analysis indicated that the AA genotype significantly reduced (more than 16 times) the risk of developing malnutrition.
Fernandes MR, et al. 2021[19].	216 patients, 92 with anatomopathological diagnosis of gastric cancer and 124 of colorectal cancer	To analyze 33 polymorphisms in 17 drug-genes involved with fluoropyrimidines in patients with gastrointestinal cancer.	Four polymorphisms of the *ABCC4*, *FPGS*, *SLC29A1*, and *MTHFR* genes are likely potential predictive biomarkers for precision medicine in fluoropyrimidine-based treatments.
Andrade RB, et al. 2023[20].	159 patients diagnosed with gastric adenocarcinoma and 193 unrelated and GC-free individuals	To investigate associations between single nucleotide polymorphisms of miRNA processing genes and GC risk in an Amazonian region.	The GG genotype of the rs10739971 variant presents a lower risk for the development of GC compared to the remaining genotypes, important to modulate genetic susceptibility to GC.
Fu L, et al. 2023[21].	220 patients with GC	To investigate the polymorphism of the TNF-α -1,031 T/C gene as an unfavorable predictor of malnutrition in patients with gastric cancer.	The SNP (-1,031 T/C) of *TNF-α* may be a useful marker in assessing the risk of nutritional deficiencies in patients with gastric cancer.
Felipe AV, et al. 2012[22].	104 patients with GC and 196 controls	To investigate the association between *IL-8* gene polymorphism (rs4073)-251A/T and gastric cancer (CG) risk	The presence of genotype A/T was associated with an increased risk of GC in the Brazilian population, whereas individuals with genotype A/A may have a protective effect on GC, and others who consume large amounts of fried foods and former smokers/smokers have a higher risk of GC.
Oliveros-Wilches R, et al. 2023[23].	59 patients with adenocarcinoma of esophagogastric function	To describe the characteristics of patients with esophagogastric junction adenocarcinoma treated at the institution, including aspects such as tumor type, treatment received, and	Different strategies are needed for an adequate diagnosis of tumors of the esophagogastric junction. Patients with type II tumors, those who received neoadjuvant, and those with a pathologic complete response had better three-year

		three-year survival outcomes.	survival.
Vinagre RMDF, et al. 2012[24].	302 patients with GC	To analyze the clinical and anatomopathological profile of gastric adenocarcinoma in patients in the northern region of Brazil. They sought to better understand the incidence, clinical and histological characteristics of this disease in this region.	The conclusion of the study highlighted that gastric adenocarcinoma mainly affects men over 60 years of age, mainly from the metropolitan mesoregion of Belém, in the State of Pará. Most cases were diagnosed in advanced stages of the disease, which required a more aggressive surgical resection.
Oliveira J.G, et al. 2012[25].	208 individuals with a diagnosis of chronic gastritis, and 174 individuals with a confirmed diagnosis of gastric cancer.	To associate deletions in the TLR4 genes (rs4986790 and rs4986791) and TLR2 (-196 to -174 del) with smoking, alcoholism, and *H. pylori* infection, and the consequent increased risk of gastric carcinogenesis	It is concluded that both the TLR2 -196 to -174 del polymorphic variant and the TLR4 +896G (Asp299Gly) polymorphic variant play a significant role in susceptibility to gastric cancer in the evaluated southeastern Brazilian population, while no association was observed for the TLR4 +1196T polymorphism.
Colombo J, et al. 2004[26].	100 patients with gastric adenocarcinoma, and 100 patients with chronic gastritis.	To test the hypothesis that, in the southeastern Brazilian population, the GSTT1, GSTM1, and CYP2E1 polymorphisms and putative risk factors are associated with an increased risk of gastric cancer.	There is no obvious relationship between the GSTT1, GSTM1, and CYP2E1 polymorphisms and gastric cancer.
Lima EM, et al. 2008[27].	The study included 66 gastric tissue samples. Of these, 20 were non-neoplastic gastric mucosa samples from patients with gastric cancer (distant from the primary tumor), and 46 were sporadic gastric cancer samples.	To establish an association between the methylation of MMR, MLH1, MSH2, MSH6, and TPM2 with gastric cancer.	PMS2 methylation was associated with both diffuse and intestinal-type cancer compared to normal controls. Intestinal-type cancer showed a significant association with MLH1 methylation. Diffuse-type cancer was significantly associated with MSH2 methylation. The findings demonstrate differential gene methylation in tumor tissue, concluding that methylation is associated with gastric carcinogenesis.
Guindalini RSC, et al. 2019[28].	88 patients with GC	To evaluate the frequency of germline CDH1 variants and diet/lifestyle habits in patients with early-onset gastric cancer	No unequivocal pathogenic germline variant of CDH1 was identified in Brazilian patients with gastric cancer. Dietary habits may be associated with the development of gastric carcinogenesis

Source: the authors

Of the 12 observational studies selected for this review, 5 were cohort studies, 6 were case-control studies, and 1 was a cross-sectional study. The duration of the intervention in the studies was three weeks for the cohort, case-control, and cross-sectional studies. The results

presented in the following tables are based on the comparison of previous blinded analyses conducted by 2 independent reviewers.

After applying the JBI tool, it was observed that, overall, the methodological quality of most studies was considered "Moderate," with a percentage score ranging from 60-90%. In the case-control studies, the average score was 79.5% (Table 2). Most cohort studies also

Citation	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Overall Rating
Oliveira JG, et al. 2012[25]	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	90% - Moderate
Colombo J, et al. 2004[26]	Y	Y	Y	Y	Y	Y	Y	Y	NC	Y	90% - Moderate
Lima EM, et al. 2008[27]	Y	NA	Y	Y	Y	N	N	Y	Y	NC	67% - Moderate
Andrade RB, et al. 2023[20]	Y	N	Y	Y	Y	Y	Y	Y	NC	Y	80% - Moderate
Felipe AV, et al. 2012[22]	Y	Y	Y	Y	Y	Y	NC	Y	NC	Y	80% - Moderate
Dantas RN, et al. 2020[17]	Y	Y	Y	Y	NC	N	N	Y	Y	Y	70% - Moderate

Y: Yes / N: No / NC: It is not clear / NA: Not applicable

Source: the authors

Table 3 - Analysis of the methodological quality for the cohort studies included with the JBI tool.

Citation	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Overall Rating
Guindalini RSC, et al. 2019[28]	N	Y	Y	Y	Y	N	Y	NA	Y	Y	Y	80% - Moderate
Fernandes MR, et al. 2021[19]	Y	Y	Y	Y	Y	N	Y	NA	N	N	Y	70% - Moderate
Oliveros-WilchesR, et al. 2023[23]	Y	Y	NA	Y	Y	Y	Y	Y	Y	NA	Y	100% - High
Fu L, et al. 2023[21]	Y	Y	Y	Y	Y	NA	Y	Y	Y	NA	Y	100% - High
Fu L, et al. 2023[18]	Y	Y	Y	Y	Y	NA	Y	NC	Y	NA	Y	89% - Moderate

Y: Yes / N: No / NC: It is not clear / NA: Not applicable

Source: the authors

Table 4 - Analysis of the methodological quality for the cross-sectional study included with the JBI tool

Citation	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Overall Rating
Vinagre RMDF, et al. 2012[24]	Y	Y	Y	Y	N	NA	Y	Y	86% - Moderate

Y: Yes / N: No / NC: It is not clear / NA: Not applicable

Source: the authors

DISCUSSION

The studies by Dantas RN et al. (2020)[17] show that the genetic protective interaction of the body in response to gastric cancer is affected due to the inactivity of tumor suppressor genes. Research on polymorphic loci is conducted in an attempt to identify potential markers that might help elucidate the molecular pathways involved in its pathogenesis[27].

According to Lima et al. (2008)[27], tissue samples from advanced gastric cancer exhibit interference in genetic instability genes, which are responsible for suppressing DNA damage and repairing tumor tissues, whether classified as diffuse gastric cancer or intestinal gastric cancer[27].

According to Guindalini et al. (2019)[28], genetic syndromes and hereditary mechanisms are associated with the types of mutations that lead to susceptibility to gastric cancer. The CDH1 gene acts as a promoter of the E-cadherin protein, which is involved in the formation of cell junctions and the maintenance of epithelial integrity. Pathogenic mutations caused by CDH1 germline variants lead to diffuse gastric cancer. Polymorphisms in the CDH1 gene, responsible for E-cadherin impairment, are directly involved in cell adhesion and the maintenance of epithelial integrity. Alterations in this gene favor epithelial-mesenchymal transition and the development of diffuse gastric carcinoma. The PSCA (Prostate Stem Cell Antigen) gene, despite its name, plays an important role in various neoplasms, including gastric cancer, where variants such as the SNP rs2976392 are consistently associated with an increased tumor risk. These results reinforce the need to incorporate the analysis of these markers into genetic screening strategies[28].

As indicated by Dantas RN et al. (2020)[17], the PSCA gene encodes proteins and may be involved in regulating cell proliferation, as well as being related to different types of cancer such as pancreatic, prostate, and gastric cancers. The SNP rs2976392 of this protein has been associated with gastric cancer risk, and its presence could indicate a potential molecular marker for the development of gastric cancer[17].

The studies by Dantas RN et al. (2020)[17] and Fu L et al. (2023)[21] highlight that TNF-alpha, a pro-inflammatory cytokine primarily involved in inflammatory and immune processes, plays a significant role in the onset and development of gastric cancer, and its SNPs are also associated with disease risk. The SNP rs1800629 has been associated with gastric cancer risk by promoting changes in transcriptional levels, affecting protein secretion in individuals[17].

The TNF-α -1031 T/C polymorphism, in addition to being associated with the risk of malnutrition in patients with gastric cancer, may represent an early marker for individualized nutritional interventions. Patients carrying the C allele, particularly those with the CC genotype, are at increased risk of weight loss and cachexia, which negatively impact chemotherapy tolerance and clinical prognosis. Pro-inflammatory cytokines, such as TNF-α and IL-8, play a

central role in gastric carcinogenesis by promoting an inflammatory microenvironment conducive to genomic instability. The IL-8 -251A/T polymorphism, for example, has been associated with increased expression of this cytokine, which may accelerate the progression of chronic gastritis to adenocarcinoma. This gene-inflammation relationship reinforces the importance of understanding the interaction between genetic factors and the immune response to Helicobacter pylori infection. Therefore, future research should not only confirm the association but also explore early nutritional screening protocols based on this marker, which could directly change care practices[21].

According to Fu L et al. (2023)[18], there is an association between the rs3917647 polymorphism of the SELP gene and malnutrition in gastric cancer. The SELP gene encodes the P-selectin protein, which is one of the main mediators of oncological malnutrition, being released through systemic inflammatory response. This study also highlighted that among gastric cancer patients, 21 were of genotype AA, 43 were of genotype AG, and 56 were of genotype GG. However, the SELP-2028(rs3917647) genotypes GG or AG showed a higher risk of malnutrition compared to genotype AA. Furthermore, when associated with other factors such as advanced age, previous surgery, male sex, and genotype GG, the risk of malnutrition is increased to varying degrees[18].

Another study conducted by Andrade RB et al. (2023)[20] analyzes the association of molecules involved in gene regulation (microRNAs), particularly the SNP pri-let-7a-1 rs1073997, with gastric cancer in the Brazilian Amazon population and highlights the polymorphism in Promoter Region Initial (PRI), which are promoter regions recognized to initiate transcription and could serve as genetic markers to prevent the incidence of metastases in this type of cancer. However, it is important to note that the highly mixed Brazilian Amazon population may not have its characteristics generalized from studies conducted in homogeneous populations[20].

Felipe AV et al. (2012)[22] elucidate the -251A/T polymorphism in the IL-8 gene, highlighting that the A/T genotype is associated with an increased risk of gastric cancer, while the A/A genotype may have a protective effect. However, no association was observed between allele frequency and gastric cancer risk. Additionally, there was no significant correlation between IL-8 genotypes and patient survival time[22].

According to studies conducted by Fernandes MR et al. (2021)[19], 33 polymorphisms in 17 drug-related genes are involved in the pharmacogenomics of fluoropyrimidines in gastric cancer patients undergoing treatment in the Brazilian Amazon. Fluoropyrimidines, especially 5-FU, are the main class of chemotherapeutic agents used to treat gastrointestinal tract neoplasms. Some SNPs contribute to drug resistance, further complicating the treatment of CG patients. Notable among these are the genes SLC29A1 (rs760370), ABCC4 (rs9524885), FPGS (rs4451422), and MTHFR (rs1801133), which are closely associated with the development of resistance and therapeutic failure during fluoropyrimidine therapies[19].

For the SLC29A1 (rs760370) gene, in addition to drug resistance, its polymorphism is associated with hematological toxicity. The ABCC4 (rs9524885) polymorphism has been described as being associated with drug toxicity, both general and severe. Furthermore, FPGS (rs4451422) has been suggested as a possible predictive marker for toxicity related to 5-FU use. The toxicity related to MTHFR (rs1801133) is not clear, but studies report this polymorphism as a risk factor for developing toxicity[19].

Due to the high degree of admixture in the Brazilian population, especially in the North region of the country, the data presented by Fernandes MR et al. (2021)[19] are unique compared to results from more homogeneous populations. The high admixture of the Brazilian population can act as a factor of genetic heterogeneity with both positive and negative implications. On the one hand, allelic diversity may confer protective profiles not yet described in specific areas. On the other hand, this same diversity makes it difficult to extrapolate results obtained from limited samples, requiring greater representation in local studies. Therefore, admixture should be considered both as a methodological challenge and as an opportunity to identify new markers of susceptibility and resistance to gastric cancer.

Despite the prospect of surgical treatment through total gastrectomy in patients with GC, the influence of intrinsic factors, which positively or negatively alter survival after surgery, is notorious. According to Oliveros-Wilches R. *et al*, (2023)[23], age is a factor directly proportional to the risk of death, increasing mortality by 5% for each year. In addition, patients classified according to the *American Society of Anesthesiology* (ASA) system as greater than II and those undergoing multivisceral resection (extended gastrectomy) have a more significant morbidity and mortality[27].

As demonstrated by Colombo J et al. (2004)[26], some studies have revealed the involvement of polymorphisms in metabolic and DNA repair enzymes, such as GSTM1 and GSTT1, which may contribute to cancer susceptibility. Among these enzyme polymorphisms, those of cytochrome P-450 (CYPs), particularly CYP2E1, stand out. However, the gene polymorphisms alone do not have risks directly associated with GC. Although no direct association with gastric cancer has been shown, the null genotype of GSTM1 combined with smoking appears to increase the risk of developing gastric cancer. This supports previous studies indicating the importance of considering environmental factors, such as smoking, when investigating genetic susceptibility to gastric cancer[26].

Furthermore, studies by Oliveira JG et al. (2012)[25] demonstrate that, in the field of molecular oncology, genetic variations in the TLR2 and TLR4 genes may influence susceptibility to gastric cancer in a Brazilian population. These genes are part of the innate immune system and play a crucial role in the inflammatory response against Helicobacter pylori, potentially modifying the immune response, increasing inflammation, and consequently increasing the risk of progression of gastric lesions to cancer. The higher frequency of variant alleles in individuals with GC suggests that these polymorphisms may serve as genetic risk markers for the disease, especially when combined with environmental factors such as alcohol consumption, indicating a significant gene-environment interaction[25]. The poor nutrition reported in cancer patients should not be understood solely as a consequence of neoplasia, but also as a modulator of the intestinal and gastric microbiota. Changes in microbial balance can favor the persistence of pro-inflammatory bacteria, such as *H. pylori*, increasing the risk of carcinogenesis. This interaction suggests that polymorphisms related to the immune response against pathogens may also indirectly influence nutritional status and, consequently, the clinical outcome of patients.

Drug resistance is a significant challenge in the treatment of gastric cancer. Polymorphisms in the ABCC4, FPGS, SLC29A1, and MTHFR genes have been shown to be associated with treatment failures related to the use of fluoropyrimidines. These variants affect everything from drug absorption and transport to drug metabolism, compromising its efficacy. Identifying these genetic markers in Latin American patients could enable the implementation of pharmacogenomic protocols, with individualized dose adjustments and the selection of more effective therapeutic regimens[19].

The reviewed studies allow us to distinguish polymorphisms with potential roles as susceptibility markers, such as those in the PSCA gene and pro-inflammatory cytokines, from those associated with prognosis and therapeutic response, such as ABCC4 and MTHFR. This differentiation is essential for future work to better direct the use of biomarkers in both population screening and individualized clinical practice[19].

Finally, a study by Vinagre RMDF (2012)[24] showed that the diagnosis of gastric cancer predominantly occurs at a late stage, particularly in patients around the sixth decade of life and predominantly in males, with a higher frequency of advanced-stage IIIB adenocarcinoma tumors. The incidence was related to the patients' dietary and lifestyle habits. Due to the advanced staging in most patients at diagnosis, more invasive procedures were necessary, with total gastrectomy being the chosen therapeutic plan in many cases. However, it is worth noting that there was no significant difference between other types of surgery[24].

Despite the prospect of surgical treatment through total gastrectomy in GC patients, the influence of intrinsic factors, which can positively or negatively affect postoperative survival, is notable. According to Oliveros-Wilches R. et al. (2023)[23], age is directly proportional to the risk of death, increasing mortality by 5% for each additional year. Additionally, patients classified according to the American Society of Anesthesiology (ASA) system as greater than II and those undergoing multivisceral resection (extended gastrectomy) present a more pronounced morbidity-mortality profile[27].

CONCLUSION

In summary, this systematic review demonstrated that the risk and development of gastric cancer (GC) in the Brazilian population are significantly linked to a combination of genetic polymorphisms, inflammatory profiles, and environmental factors. The main impact of this study lies in the identification of genetic biomarkers with potential immediate clinical application. Polymorphisms in the CDH1, TLR2, and TLR4 genes (linked to the inflammatory response) can serve as genetic risk markers, establishing a solid foundation for personalized screening of individuals with high susceptibility. Furthermore, the identification of SNPs in genes such as SLC29A1, ABCC4, FPGS, and MTHFR is directly associated with therapeutic resistance to fluoropyrimidines. This finding supports the development of pharmacogenomic tests that can optimize chemotherapy choice and reduce treatment failure, especially

considering the specificities of regional admixture. The urgency of the problem is reinforced by our observation that diagnosis is predominantly late, highlighting the need to incorporate genetic knowledge for earlier detection and continuous improvement of care strategies.

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ASSOCIATION OF POLYMORPHISMS IN GASTRIC CANCER IN LATIN AMERICAN INDIVIDUALS: A BRIEF SYSTEMATIC REVIEW

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