

## Single nucleotide polymorphisms in the *IGFBP3* gene and the carcinogenesis process: a systematic review

Polimorfismos de nucleotídeos único no gene *IGFBP3* e o processo de carcinogênese: uma revisão sistemática

Polimorfismos de nucleótidos único en el gen *IGFBP3* y el proceso de carcinogénesis: una revisión sistemática

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### **Abstract**

Introduction: Insulin-like growth factor binding protein -3 (IGFBP3) is the main mediator of IGF-1/IGF-1R binding, and may inhibit the binding between IGF-1 and IGF-1R and trigger cell growth suppression. Method: This study is a systematic review in which searches were conducted in Pubmed, Web of science, Science direct and Scopus databases for studies published in the period 2010-2020, including case-control studies that evaluated the association of polymorphisms in the *IGFBP3* gene with cancer. Results: Of the 6 studies included, 5 were conducted in China and 1 in Iran, published in 2015 (n=2), 2014 (n=2), 2013 (n=1) and 2011 (n=1). In all, there were 5 types of cancer studied: esophagus (n=2), prostate (n=1), colorectal (n=1), breast (n=1) and gastric (n=1). In the studies chosen, 8 SNPs located in the *IGFBP3* gene were evaluated: rs2854744, rs2854746, rs2132572, rs9282734, rs3110697, rs2960436, rs2270628 and rs10282088. Only the Zhao et al studies. (2015) and Liu et al. (2015) found a relationship between SNPs in the *IGFBP3* gene with cancer. Two studies (Qian et al., 2014 and Qian et al., 2011) did not describe allelic frequencies in their results. Conclusion: Based on the studies we can demonstrate that the findings on the association of polymorphisms in the *IGFBP3* gene with cancers are confusing, divergent and the role of the IGF pathway in carcinogenesis has not

been clearly defined. However, the studies bring strong evidence that suggests possible relationships of this pathway and genetic variants with the carcinogenesis process in several types of cancer.

**Keywords:** SNPs; Insulin-like growth Factor-binding protein 3; Cancer.

### Resumo

**Introdução:** A proteína de ligação do fator de crescimento semelhante à insulina -3 (IGFBP3) é a principal mediadora da ligação IGF-1/IGF-1R, podendo inibir a ligação entre IGF-1 e IGF-1R e desencadear a supressão do crescimento celular. **Método:** Este estudo é uma revisão sistemática na qual foram realizadas pesquisas em bancos de dados *Pubmed*, *Web of Science*, *ScienceDirect* e *Scopus* para estudos publicados no período 2010-2020, incluindo estudos de caso-controle que avaliaram a associação de polimorfismos no gene *IGFBP3* com câncer. **Resultados:** Dos 6 estudos incluídos, 5 foram realizados na China e 1 no Irã, publicados em 2015 (n=2), 2014 (n=2), 2013 (n=1) e 2011 (n=1). Ao todo, foram estudados 5 tipos de câncer: esôfago (n=2), próstata (n=1), colorretal (n=1), mama (n=1) e gástrico (n=1). Nos estudos escolhidos, foram avaliados 8 SNPs localizados no gene *IGFBP3*: rs2854744, rs2854746, rs2132572, rs9282734, rs3110697, rs2960436, rs2270628 e rs10282088. Apenas os estudos Zhao et al. (2015) e Liu et al. (2015) encontraram uma relação entre SNPs no gene *IGFBP3* com câncer. Dois estudos (Qian et al., 2014 e Qian et al., 2011) não desprezaram frequências alélicas em seus resultados. **Conclusão:** Com base nos estudos podemos demonstrar que os achados sobre a associação de polimorfismos no gene *IGFBP3* com cânceres são confusos, divergentes e o papel da via IGF na carcinogênese não foi claramente definido. No entanto, os estudos trazem fortes evidências que sugerem possíveis relações dessa via e variantes genéticas com o processo de carcinogênese em vários tipos de câncer.

**Palavras-chave:** SNPs; Proteína 3 de ligação a fator de crescimento semelhante à insulina; Câncer.

### Resumen

La Proteína de unión al factor de crecimiento insulina-like -3 (IGFBP3) es el principal mediador de la unión a IGF-1/IGF-1R, y puede inhibir el enlace entre IGF-1 y IGF-1R y desencadenar la supresión del crecimiento celular. **Método:** Este estudio es una revisión sistemática en la que se realizaron investigaciones en bases de datos *Pubmed*, *ScienceDirect*, *Web of Science* y *Scopus* para estudios publicados en el período 2010-2020, incluyendo estudios de casos de control que evaluaron la asociación de polimorfismos en el gen *IGFBP3* con cáncer. **Resultados:** De los 6 estudios incluidos, 5 se llevaron a cabo en China y 1 en Irán, publicados en 2015 (n-2), 2014 (n-2), 2013 (n-1) y 2011 (n-1). En total, se estudiaron 5 tipos de cáncer: esófago (n-2), próstata (n-1), colorrectal (n-1), mama (n-1) y gástrico (n-1). En los estudios elegidos, se evaluaron 8 SNP ubicados en el gen *IGFBP3*: rs2854744, rs2854746, rs2132572, rs9282734, rs3110697, rs2960436, rs2270628 y rs10282088. Sólo los estudios Zhao et al. (2015) y Liu et al. (2015) encontró una relación entre los SNP en el gen *IGFBP3* con cáncer. Dos estudios (Qian et al., 2014 y Qian et al., 2011) no describieron las frecuencias alélicas en sus resultados. **Conclusión:** Sobre la base de estudios podemos demostrar que los hallazgos sobre la asociación de polimorfismos en el gen *IGFBP3* con los cánceres son confusos, divergentes y el papel de la vía IGF en la carcinogénesis no ha sido claramente definido. Sin embargo, los estudios proporcionan evidencia sólida que sugiere posibles relaciones de esta vía y variantes genéticas con el proceso de carcinogénesis en varios tipos de cáncer.

**Palabras clave:** SNPs; Proteína 3 de unión a factor de crecimiento similar a la insulina; Cáncer.

## 1. Introduction

On a global scale, cancer is the second most fatal disease in recent years. It is estimated that in 2018 there were approximately 9.6 million deaths, being lung cancers, colorectal, stomach, liver, breast, pancreas, prostate and cervical cancer cancers being the most common causes. About 70% of these deaths occurred in middle- and low-income countries (Organização Pan-Americana da Saúde/ Organização Mundial de Saúde, 2020; Global Cancer Observatory, 2020). Several factors may be associated with the disease, including immunological, genetic, environmental, socioeconomic, obesity, alcoholism, tobacco, hepatitis virus infections and human papillomavirus (HPV) (Organização Pan-Americana da Saúde/ Organização Mundial de Saúde, 2020; Meijers & De Boer, 2020).

The IGF signaling pathway (Insulin-Like Growth Factor) plays an important role in the carcinogenesis process. Insulin-like growth factor binding protein -3 (IGFBP3) is the main mediator of IGF-1/IGF-1R binding, and may inhibit the binding between IGF-1 and IGF-1R and trigger cell growth suppression. This protein, together with the other IFGs, are involved in cancer signaling networks, acting in suppression, cell proliferation, induction to programmed cell death and playing roles in normal and/or malignant cell growth processes. These characteristics demonstrate that the IGF signaling pathway is related to the development of cancer (Tang et al., 2019; Wang et al., 2018; Chen et al., 2018).

Studies have found the association of single nucleotide polymorphisms in the *IGFBP3* gene with the risk of different

cancer types (Qin et al., 2016; Zhang et al., 2016; Terry et al., 2009; Zhao et al., 2015; Liu et al., 2015). In addition, polymorphisms in this gene were associated with changes in circulating levels of IGFBP3 and IGF-1 (Bonilla, et al. 2016). In another study, an association was identified between circulating levels of IGFBP3 and the risk of colorectal cancer (Murphy et al., 2020). In view of this scenario, this study aimed to conduct a systematic review of the literature on the relationship between polymorphisms in the *IGFBP3* gene and the risk of developing cancer.

## 2. Methodology

The present study is a systematic review of the literature, with a qualitative approach, in which descriptive data of the articles included are presented and their results are interpreted collectively with the specific instruments (Pereira, Shitsuka, Parreira, & Shitsuka, 2018). A previous search was conducted in the International Register of Ongoing Systematic Reviews (PROSPERO) and Cochrane, to verify the existence of other reviews of the same thematic nature and, by discarding the existence, we recorded the protocol of this review, registration number CRD42020187924. The searches were carried out in May 2020 in the databases PUBMED, Web of Science, ScienceDirect and Scopus for papers published in the period 2010-2020.

The following research question: "single nucleotide polymorphisms in the *IGFBP3* gene are involved in the carcinogenesis process?", was elaborated based on acronymical of PICOS with Population (P): cancer patients; Intervention (I): presence of single nucleotide polymorphisms in the *IGFBP3* gene; Comparator (C): healthy patients; Outcome (O): risk assessment or protection of SNPs in the *IGFBP3* gene in relation to carcinogenesis; Study design (S): case-control; Additional results: identify the most polymorphism-related types of cancer in the *IGFBP3* gene. The search strategy of this research used descriptors and Boolean operators: (SNP OR "simple nucleotide polymorphism" OR "single nucleotide polymorphism") AND (IGFBP3 OR "insulin-like growth factor binding protein 3") AND (neoplasm OR cancer) AND ("case-control" OR "case-control study").

For the selection of articles, inclusion criteria were used: original articles, case-control studies that evaluated the association of SNPs in the *IGFBP3* gene with cancer and without language restrictions. Exclusion criteria were: review articles, those that do not answer the research question and studies with quality score/level (check list Downs and Black) less than 20, reasonable quality.

Search results were recorded in Spreadsheet in Microsoft Office Excel 2019 and selected according to the recommendations of the Preferred Reporting Items for Systematic Reviews (PRISMA), either with the application of the selection criteria cited. The records identified from the searches had duplicates removed and were analyzed first by reading the title and abstract, where the selection was made. Next, full-text reading was performed and articles that were not within the inclusion criteria were excluded. The evaluations and data extraction were performed by three evaluators (IFS, PPF e DMS). The conflicts were resolved from the discussion with the third evaluator (DMS).

The methodological quality and risk of bias of the selected studies were analyzed using the Check-list Downs and Black, with score range for corresponding quality levels: Excellent (26-28); Good (20-25); Reasonable (15-19) e Bad ( $\leq 14$ ). From the scores, only studies with good and excellent quality levels were selected. The methodological quality was analyzed by two researchers (PPF e IFS). There were no inconsistencies in the methodological evaluation, so there was no need for a third evaluation. Questions 14, 15 and 19 of the bias domain were not considered, as they do not apply to case-control studies, so all studies were scored in these questions with the purpose of not harming the score range and evaluation.

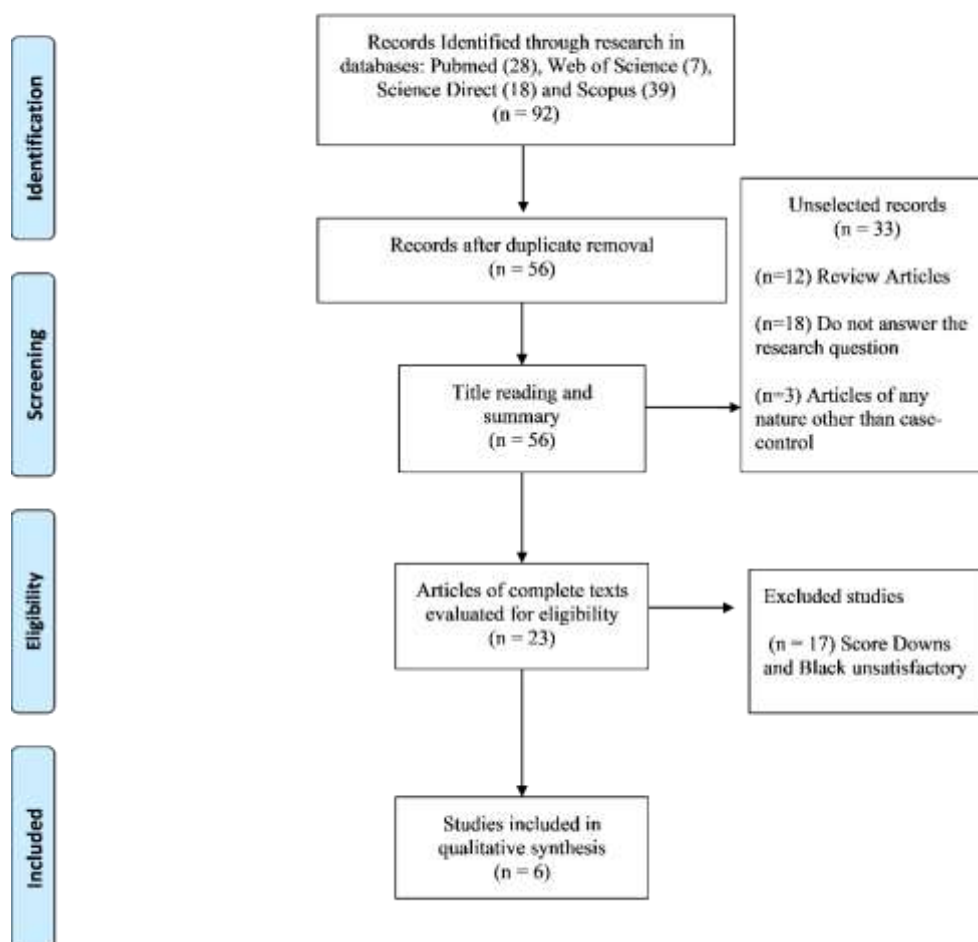
The data extraction of the articles chosen followed with information that portrayed the characteristics of the studies: name of the first author, year of publication, country, ethnicity, type of cancer, polymorphism evaluated, study objective, genotyping method, sampling technique, mean age of cases and controls, number of the general sample and by subgroups, gender, main conclusions, genotypic frequencies, allele frequency, genetic models, Odds Ratio (OR), P-value Hardy-Weinberg

equilibrium (HWE).

### 3. Results and Discussion

Using the search strategy in the databases, a total of 92 articles were identified. During the selection and application stage of the eligibility criteria, 86 articles were removed from the evaluation. Of these, 36 were duplicated, 12 were revisions, 18 did not answer the question of this research and 3 were not case-control studies (Figure 1).

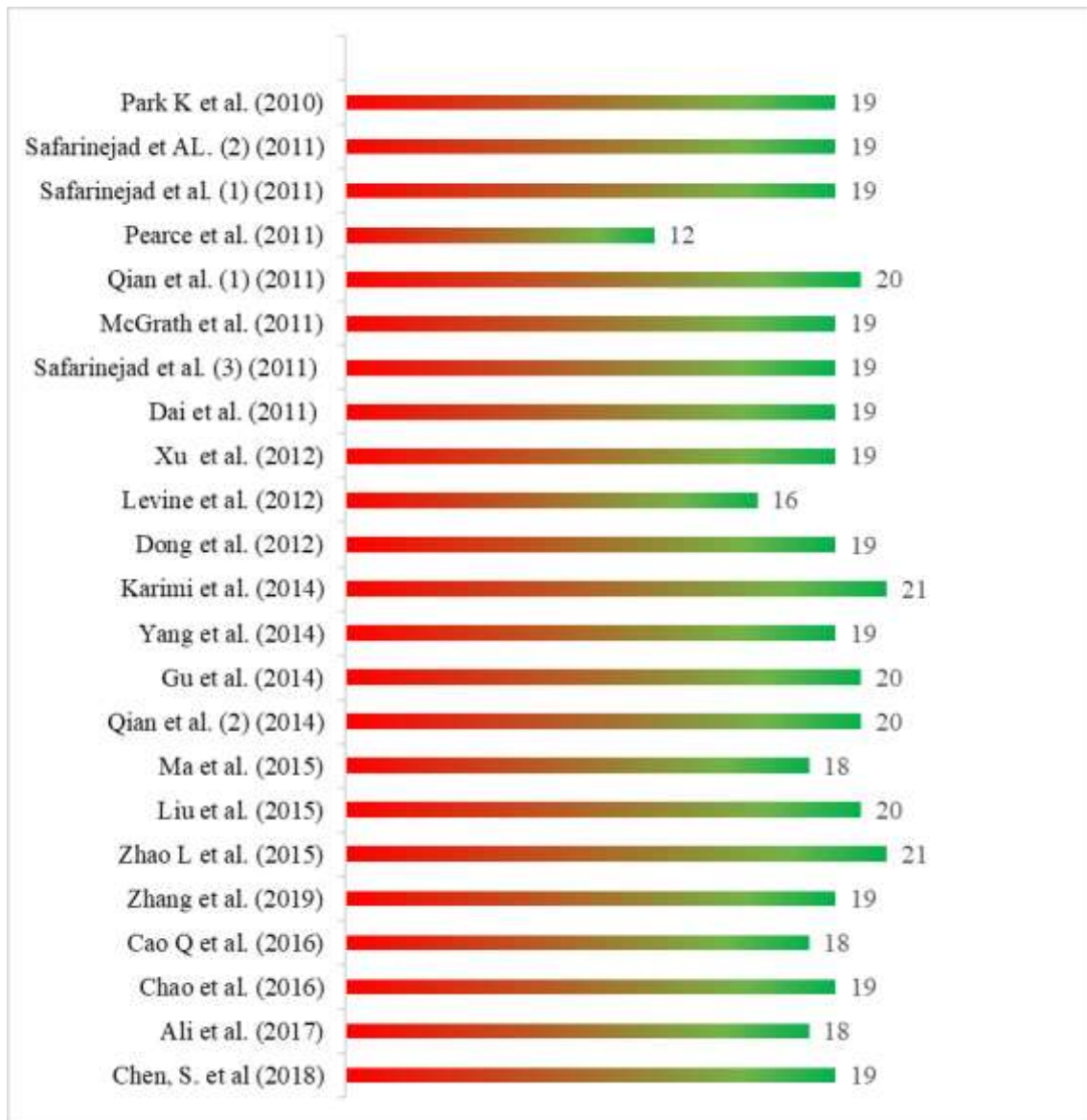
**Figure 1** - Flow chart of study selection.



Source: Authors (2020).

Of the 23 articles selected for reading full texts and applying the Check-list Downs and Black, 17 were excluded for not having obtained a score equivalent to good quality (20-25) or excellent (26-28), being 16 with reasonable quality (15-19) and 1 article with quality of "bad" ( $\leq 14$ ). Were included at the end of the selection stage 6 articles that met the inclusion values (Zhao et al., 2015; Qian et al., 2014; Karimi et al., 2013; Qian et al., 2011; Gu et al., 2014; e Liu et al., 2015) (Figure 2).

**Figure 2** - Assessment of methodological quality and risk of bias through the checklist Downs and Black.



Legend: Quality levels - Excellent (26-28); Good (20-25); Reasonable (15-19) and Bad ( $\leq 14$ ). Source: Authors (2020).

The characteristics of the included studies are presented in Table 1. Of the 6 studies included, 5 were conducted in China and 1 in Iran, published in 2015 (n=2), 2014 (n=2), 2013 (n=1) and 2011 (n=1). In all, there were 5 types of cancer studied: esophagus (n=2), prostate (n=1), colorectal (n=1), breast (n=1) and gastric (n=1). In the studies chosen, 8 SNPs located in the *IGFBP3* gene were evaluated: rs2854744, rs2854746, rs2132572, rs9282734, rs3110697, rs2960436, rs2270628 and rs10282088. The Genotyping methods included: PCR-RFLP, RT-PCR and Multiplex PCR (Table 1).

**Table 1** - Characteristics of the studies included in the systematic review.

Author	Year	Country	Ethnicity	Type of cancer	SNP	Objective	Genotyping method	Sampling technique	Average age $\pm$ SD		N	Gender	Conclusion
									Casos	Controls			
Zhao et al.	2015	China	Han	Esophagus	rs2854744 rs2854746	Clarify the association between SNP IGFBP-3 (A > C), rs2854746 (G > C) and risk of esophageal cancer	Multiplex PCR	Case Series	58,33 $\pm$ 2,21	59,82 $\pm$ 3,27	238	M e F	Polymorphism in IGFBP-3 rs2854744 A > C may be a potential predictor of esophageal cancer risk and patient survival.
Qian et al.	2014	China	Han	Prostate	rs2132572 rs2854744 rs2854746 rs9282734	Assess the association of the five SNPs on <i>IGF-I</i> (rs6214, rs6218, rs35767, rs5742612, rs5742714) and four SNPs in the <i>IGFBP-3</i> (rs2132572, rs2854744, rs2854746, rs9282734) with prostate cancer in the Chinese population	RT-PCR	Case Series	57,50 $\pm$ 8,00	71,30 $\pm$ 7,40	1.366	M	The results indicate that the three SNPs (rs6218, rs35767 and rs5742612) and articular genotypes with 2 to 6 risk alleles can contribute to susceptibility to prostate cancer, but not progression, in the Chinese population.
Karimi et al.	2013	Iran	-	Colorectal	rs3110697	Understand the association of SNPs in various genes related to insulin pathway and the risk Colorectal cancer	PCR-RFLP	Case Series	53.88 $\pm$ 13.45	42.38 $\pm$ 15.40	444	M e F	These findings do not support plausible associations between polymorphic variations in the <i>IGFBP-3</i> gene and risk of colorectal cancer.
Qian et al.	2011	China	-	breast	rs2854746 rs2960436	Analyze breast cancer risk associations with four IGF-I SNPs and two IGFBP-3, and examine the correlation between IGF-I and IGFBP-3 genotypes and their phenotypes in breast tumor tissues	RT-PCR	Case Series	-	-	806	F	Patients with wild IGF-I or IGFBP-3 variant genotypes had higher levels of IGF-I peptides compared to those with wild IGF-I or IGFBP-3 variants.
Gu et al.	2014	China	-	Gastric	rs2854744	Evaluate the independent and combined effects of IGF2 and <i>IGFBP3</i> genotypes at risk Gastric Cancer.	RT-PCR	Case Series	60,3 $\pm$ 16,9	58,5 $\pm$ 15,9	828	M e F	The results suggest that polymorphic variants of IGF2 genes modulate gastric carcinogenesis. In addition, when IGF2 and <i>IGFBP3</i> variants are evaluated together, a greater effect on the risk of CG is observed.
Liu et al.	2015	China	-	Esophagus	rs2270628 rs10282088 rs3110697	to investigate the association between IGFBP-3 genotypes and susceptibility of esophageal cancer	RT-PCR	Case Series	62,84 $\pm$ 8,50	63,44 $\pm$ 7,19	760	M e F	There was a relationship of decreased risk for esophageal cancer in the three SNPs (rs2270628 C > T, rs10282088 C > A and rs3110697 G > A)

Legend: RT-PCR (PCR real time). Source: Authors (2020).

One of the weaknesses detected in the studies by Zhao et al., 2015; Liu et al., 2015; Qian et al., 2014; Gu et al., 2014; Karimi et al., 2013 and Qian et al., 2011 was the lack of representativeness of the sampling power (Table 2). This analysis is an important aspect in molecular epidemiology studies, as it is able to determine the efficacy of the prediction presented in the study. Another weakness was that of the domain "External Validity", with regard to the representativeness of the population studied. The maximum score of this domain was 1 in three studies, on a scale from 0 to 3, constituting studies of low sample representativeness (Table 2). On the other hand, all the studies included scores in all categories of the reporting domain.

**Table 2** – Assessment of the risk of bias and methodological quality of studies through the Check-list Downs and Black.

Studies	Domains						
	Year	Report	External Validity	Bias	Selection Bias	Power	Total
<b>Zhao et al.</b>	2015	10	1	6	4	0	21
<b>Liu et al.</b>	2015	10	0	6	4	0	20
<b>Qian et al.</b>	2014	10	0	6	4	0	20
<b>Gu et al.</b>	2014	10	0	6	4	0	20
<b>Karimi et al.</b>	2013	10	1	6	4	0	21
<b>Qian et al.</b>	2011	10	1	6	3	0	20

Source: Authors (2020).

No study showed deviation from HWE. Only Zhao et al studies. (2015) and Liu et al. (2015) found a relationship between SNPs in the *IGFBP3* gene with cancer. Two studies (Qian et al., 2014 and Qian et al., 2011) did not describe allelic frequencies in their results. In addition, only the study by Karimi et al. (2013) presented all genetic models.

Circulating IGFBP3 levels and G allele of the Polymorphism rs11977526 G>A of the *IGFBP3* gene were associated with the risk of colorectal cancer in a study based on serological analyses and mendelian randomization (MURPHY et al., 2020). The meta-analysis of Wang et al. (2018) also found a relationship between rs2854746 C>G polymorphism with colorectal cancer, with the G allele being associated with the increased risk for this type of cancer (Wang et al., 2018)

In the study by Zhao et al. (2015) possible associations of rs2854744 polymorphism with esophageal cancer were evaluated in a sample of 238 participants (cases=110 and controls=128). The C/C genotype of SNP rs2854744 was related to increased susceptibility to esophageal cancer when compared to homozygous A/A (p=0,044; OR adjusted =1,328 [CI=0,934–1,855]). The C variant of this same SNP also showed a statistically significant result associated with susceptibility to esophageal cancer (p=0,032; OR=1.201 [CI=1.014-1.423]. In two other studies included in this review, Qian et al. (2014) and Gu et al. (2014), the association of SNP rs2854744 with prostate and gastric cancers, respectively, was also evaluated, but no association was found.

In two other studies included in this review, Qian et al. (2014) and Gu et al. (2014), the association of SNP rs2854744 with prostate and gastric cancers, respectively, was also evaluated, but no association was found. On the other hand, in another meta-analysis that included 10 studies (9,415 cases and 14,179 controls), the authors evaluated a possible association of the same variant with susceptibility to colorectal cancer, but did not find a significant relationship (Wan et al., 2018). This demonstrates that there are still divergences in the literature on the role of SNP rs2854744 in the carcinogenesis process.

The study by Liu et al. (2015) conducted in China, with 760 participants (cases=380 and controls=380), evaluated possible relationships of SNPs rs2270628, rs10282088 and rs3110697 with esophageal cancer. The C/T genotype of SNP

rs2270628 was related to the reduced risk of esophageal cancer when compared to genotype C/C (p adjusted= 0,033; OR adjusted= 0.70[CI=0.50-0.97]). For SNP rs10282088, genotype C/A, compared to genotype C/C, was statistically significant, with a reduction in the risk for esophageal cancer (p adjusted= 0,002; OR adjusted= 0.54 [CI=0.39-0.74]). According to the author, this was the first study that evaluated the association of this SNP with esophageal cancer. In addition, when compared to the ancestral genotype G/G, the G/A genotype of SNP rs3110697 was associated with reduced risk of esophageal cancer (p adjusted= 0,003; OR adjusted = 0.63[0.46-0.86]). Still in this same SNP, the A allele was also statistically associated with a lower risk of developing esophageal cancer (p= 0,012; OR= 0.74[CI=0.58-0.93]). The study by Karimi et al. (2013) also evaluated the possible association of the rs3110697 variant with colorectal cancer, but it was not possible to identify results that proved a statistically significant relationship.

In the study by Terry et al. (2009) the T allele of polymorphism rs2270628 C>T was associated with increased risk of ovarian cancer. However, in the study by Chen et al. (2018), conducted with 521 patients and 1,030 controls in a Chinese Han population, the relationship between SNP rs2270628 and susceptibility to lung cancer found no associations of this polymorphism with lung cancer. The Study Tang et al. (2019) performed with 720 cases of Esophagogastric Junction Adenocarcinoma (EGJA) and 1541 controls were also not found a statistically significant relationship for the risk of Esophageal Gastric Junction Adenocarcinoma (EGJA). The SNP rs2854746 was evaluated in three of the included studies (Zhao L et al., 2015; Qian et al., 2014 and Qian et al., 2011) and there were no significant statistical associations with esophageal, prostate and breast cancer, respectively.

In this review it was not possible to perform a meta-analysis due to the studies chosen evaluating different types of cancers and SNPs, and consequently high heterogeneity. As a gap, most articles did not bring allele frequency or genetic models, representative sampling power, besides having presented low methodological quality.

#### 4. Conclusion

This review identified two studies (Zhao et al. (2015) and Liu et al. (2015)) who presented evidence of statistically significant relationships of association of SNPs rs2854744, rs10282088 and rs3110697 with esophageal cancer. Based on the studies, we can demonstrate that the findings on the association of polymorphisms in the *IGFBP3* gene with cancers are confusing, divergent and the role of the IGF pathway in carcinogenesis has not been clearly defined. However, the studies bring strong evidence that suggests possible relationships of this pathway and genetic variants with the carcinogenesis process in various types of cancer.

In addition, our study suggests case-control studies or cohorts with more significant samples to clearly investigate the possible associations of polymorphisms in the *IGFBP3* gene and susceptibility to the development of the various types of cancer.

#### Suggestions

For future studies, we suggest that the ad hoc sampling power test be performed in order to obtain, previously, the appropriate sample number for statistical significance in the study population. It is also suggested the presentation of all genetic models in the results (codominant, dominant, recessive and overdominant) so that it is possible to have a broader view of the results obtained and minimize the reporting bias.

In addition, it is important to conduct studies evaluating serum IGFBP3 levels and susceptibility to cancer or worsening of the disease. We emphasize the importance of the control groups being healthy participants, without a history of cancer, and that the presence of comorbidities that influence the risk of cancer development are controlled in the selection.



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