IL1B -511 polymorphism and association with susceptibility and prognosis in patients with papillary thyroid carcinoma

Polimorfismo IL1B -511 e associação com suscetibilidade e prognóstico em pacientes com carcinoma papilífero de tireoide

IL1B -511 polimorfismo y asociación con susceptibilidad y pronóstico en pacientes con carcinoma papilar de tiroides

Vinícius Guimarães Pessoa[1], Larissa Sousa Silva Bonasser[2], Jéssica Nayane Gomes de Souza[3], Renata de Souza Freitas[4], Calliandra Maria de Souza Silva[5], Rafael Martins de Morais[6], Jamila Reis de Oliveira[7], Izabel Cristina Rodrigues da Silva[8]

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REVISA

1. University of Brasilia, Ceilândia College. Ceilândia, Distrito Federal, Brazil. https://orcid.org/0000-0003-2832-0527

2. University of Brasilia, Ceilândia College. Ceilândia, Distrito Federal, Brazil. https://orcid.org/0000-0002-7812-8026

3. University of Brasilia, Ceilândia College. Ceilândia, Distrito Federal, Brazil. https://orcid.org/0000-0002-0769-3829

4. Catholic University of Brasilia. Taguatinga, Federal District, Brazil. https://orcid.org/0000-0003-3563-6415

5. University of Brasilia, Ceilândia College. Ceilândia, Distrito Federal, Brazil. https://orcid.org/0000-0002-9064-0735

6. Syrian-Lebanese Hospital. Brasília, Distrito Federal, Brazil https://orcid.org/0000-0003-0777-9494

7. University of Brasilia, Ceilândia College. Ceilândia, Distrito Federal, Brazil. https://orcid.org/0000-0002-9577-0344

8. University of Brasilia, Ceilândia College. Ceilândia, Distrito Federal, Brazil. https://orcid.org/0000-0002-6836-3583

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RESUMO

Objetivo: Associar a presença do SNP IL1B -511 (rs16944) à susceptibilidade ao CPT, bem como comparar níveis séricos da citocina antes e sete dias após a Iodoterapia, juntamente com outras características clínicas dos pacientes. **Método:** Trata-se de um estudo caso-controle, no qual foram obtidas amostras de sangue de 52 indivíduos (26 em cada grupo). A genotipagem foi realizada por meio da estratégia PCR-RFLP. Os níveis séricos de IL-1β foi medido por meio de kit para ensaio imunoenzimático (ELISA). Testes para médias e estudos de associação foram executados considerando-se um nível de significância de 5%. **Resultados:** Não houve diferença estatística com relação a distribuição genotípica entre indivíduos caso e controle, e estes grupos não diferiram em relação às dosagens de citocina. Porém, os níveis de citocina aumentaram significativamente após a Iodoterapia, sendo que os portadores do genótipo CC apresentaram maior produção da proteína, mas este aumento não estava correlacionado com a dose de radiofármaco administrada**. Conclusão:** O polimorfismo IL1B -511 não foi associado à susceptibilidade ao CPT, porém os níveis séricos da citocina elevaram-se com o tratamento da iodoterapia, e esta elevação foi genótipo dependente.

Descritores: Câncer de tireoide; Radioisótopos do iodo; Interleucina-1 beta; Polimorfismo genético.

ABSTRACT

Objective: To associate the presence of SNP IL1B -511 (rs16944) with susceptibility to TLC, as well as to compare serum cytokine levels before and seven days after iodotherapy, along with other clinical characteristics of patients. **Method:** This is a case-control study, in which blood samples were obtained from 52 individuals (26 in each group). Genotyping was performed using the PCR-RFLP strategy. Serum IL-1β levels were measured using an enzyme immunoassay kit (ELISA). Tests for means and association studies were performed considering a significance level of 5%. **Results:** There was no statistical difference regarding genotypic distribution between case and control individuals, and these groups did not differ in relation to cytokine dosages. However, cytokine levels increased significantly after iodine therapy, and patients with the CC genotype showed higher protein production, but this increase was not correlated with the administered radiopharmaceutical dose. **Conclusion:** IL1B-511 polymorphism was not associated with susceptibility to TLC, but serum cytokine levels increased with the treatment of iodotherapy, and this elevation was genotype dependent.

Descriptors: Thyroid cancer; Iodine radioisotopes; Interleukin-1 beta; Genetic polymorphism.

RESUMEN

Objetivo: investigar la asociación entre el polimorfismo VNTR del gen IL4, localizado en la región intrón 3, en pacientes diagnosticados de accidente cerebrovascular hemorrágico (Stroke) o aneurisma intracerebral en una muestra del Distrito Federal. **Método:** Estudio observacional, retrospectivo, transversal, con 55 individuos, del cual se registraron las características clínicas de las historias clínicas y se realizó un análisis de genotipado mediante la estrategia de PCR. Las frecuencias genotípicas se estimaron mediante conteo directo. El nivel de significancia adoptado fue del 5% y la prueba estadística utilizada fue Chi-Cuadrado. **Resultados:** Se verificó que el genotipo más frecuente fue B1/B2 (50,9%; n=28), seguido del genotipo ancestral B1/B1 (27,3%, N=15), y el menos frecuente fue el genotipo B2/B2 (21,8%, N=12). No se encontró asociación estadística entre las variables hipertensión arterial sistémica, diabetes, tabaquismo y consumo de alcohol y la presencia de polimorfismo en el grupo estudiado. **Conclusión:** La presencia del polimorfismo IL4 INTRON 3 VNTR se asoció con la variable género, demostrando que en la muestra estudiada, AVEH es más frecuente en mujeres que en hombres, divergiendo de los estudios en los que los varones tienen más probabilidades de desarrollar una VENa.

Descriptores: Polimorfismo; Interleucina-4; Accidente cerebrovascular hemorrágico.

ORIGINAL

Introduction

Papillary thyroid carcinoma (PTC) is the most common form of thyroid cancer and is usually associated with previous exposure to ionizing radiation. Solitary or multifocal lesions within the thyroid may be manifestations of this type of neoplasm. Lesions are often cystic and may contain areas of fibrosis and calcification. The definitive diagnosis is made by means of microscopy, which is based on the nuclear characteristics of the cell.[1]

The most used treatment for PTC, and considered as the first choice, consists of surgical removal of the thyroid gland, clinically called thyroidectomy, later complemented with ablation by the radiopharmaceutical Iodine^{131}, also called Radioactive Iodine.[2] Through this radiopharmaceutical, permanent remission is possible of the tumor in most patients, since in differentiated tumors such as PTC, there is maintenance of I131 uptake proteins, allowing their entry into the follicular cell and with consequent destructive action on target cells.[3]

Although thyroid cancer is considered the most common neoplasm of the head and neck region, retrospective survey studies show that the initial detection of carcinoma occurs only in the identification of metastases in cervical lymph nodes.[4]

The emergence of high-performance sequencing technologies based on the occurrence of new molecular abnormalities allowed the evolution of knowledge about the molecular diagnosis of various cancers. Molecular markers of thyroid cancer are found in more than 70% of differentiated carcinomas and the understanding of its diverse molecular mechanisms is favorable to new perspectives for its diagnosis and treatment.[5]

In this sense, molecular markers for inflammatory pathways have gained prominence for the understanding of tumor biology, given that inflammation is an important component of the tumor microenvironment.6 Among the markers, cytokines are mentioned, which act in the immune system to send stimulatory, modulatory and/or inhibitory signals.[7]

Interleukin-1 (IL-1) is a polypeptide considered as the main mediating agent in the immune response against inflammation. Among the interleukins belonging to the IL-1 family are IL-1α, IL-1β and IL-1Ra.[8] These cytokines have differences regarding their immune function, since there are pro-inflammatory ones, represented by IL-1α and IL-1β, in addition to the anti-inflammatories represented by IL-1RA.[9]

In diseases characterized by the occurrence of an acute or chronic inflammatory process, IL-1β together with other pro-inflammatory cytokines can induce the body to create a series of responses, including fever, increased protein synthesis by the liver, increased release of corticosteroids, changes in the brain activity of monoamines, hyperalgesia, among others.[10,11]

The rs16944 genotype is used to refer to the SNP (Single Nucleotide Polymorphism) in the promoter region of the IL-1β gene. rs16944 has been associated with multiple diseases such as schizophrenia, 12 osteoarthritis, 13 diabetes, 14 chronic rhinosinusitis, 15 Graves' ophthalmopathy, 16 angular glaucoma, 17 gastric adenocarcinoma 18 and breast cancer.[19]

With this, the objective of the study was to associate the presence of IL1B -511 polymorphism (rs16944) with susceptibility to papillary thyroid carcinoma

(PTC) and to describe the difference in serum levels of the cytokine before and after iodotherapy, in addition to other clinical characteristics.

Method

Samples were obtained from a hospital-based case-control study completed in six months (June to December 2017). For this, the sample was calculated by estimating the prevalence of 1% of thyroid cancer among the types of cancer in the adult population, sampling error of 5% and confidence interval (CI) of 95%, where in a number of patients n = 8450, reaching 12 participants. With loss compensation, a sample of 26 PTC patients was considered. Therefore, this study was composed of 26 individuals in the case group (16 women and 10 men; mean age 48 years ± 13 years). The control group consisted of 26 participants (17 women and 9 men, mean age 46 years ± 7 years), and this group consisted of healthy, voluntary, matched individuals who were recruited and also healthy individuals accompanying patients in the general department of outpatients (OPD).

The inclusion criteria for the case group were: patients of both sexes, aged over 18 years, diagnosed with thyroid cancer and who underwent radioiodine therapy at the Nuclear Medicine Medical Images Service of Brasília (IMEB). For the control group, the inclusion criteria were: individuals of both genders, who did not have carcinoma, did not undergo radioiodine therapy and had no degree of kinship with the patients in the case group. In both groups, participants were excluded if they were younger than 18 years old, if they had a diagnosis of thyroid cancer, but were not eligible for radioiodine therapy, in addition to those who did not accept to participate in the research or when legal representatives did not consent to participate. The patients' clinical data were recorded according to information collected from the medical records.

This study was approved by the Research Ethics Committee of the Centro Universitário de Brasília - UNICEUB, under opinion nº 1.965.528, CAAE nº 57382416.6.0000.0023. All participants signed the Free and Informed Consent Form (TCLE) before the study was carried out.

The samples were collected in their entirety by venipuncture for DNA isolation. DNA was extracted from peripheral blood using the PureLink® Genomic DNA Mini Kit, from Invitrogen (Waltham, Massachusetts, USA; catalog #K1820-02, batch #19339891). DNA concentration was determined by electrophoretic running on a 2% agarose gel, stained with ethidium bromide. The average yield achieved was 20 ng/µL. Then, the diluted DNA was submitted to the PCR (Polymerase Chain Reaction) technique to study the distribution of SNPs. The oligonucleotide sequences used to evaluate the polymorphisms were respectively: rs16944 F 5'-TGG-CAT-TGA-TCT-GGT-TCA-TC-3' and rs16944 R 5'-GTT-TAG-GAA-TCT-TCC-CAC -TT-3'.

The thermocycling conditions were 94°C for 5 minutes (initial denaturation), followed by 45 cycles of denaturation at 94°C for 1 minute, annealing of the oligonucleotides at 55°C for 1 minute and 72°C for 1 minute for extension of the fragments. Final extension was performed at 72°C for 7 minutes and cooling for 4 minutes. The equipment used was the Techne Thermal Cycler model TC-512.

In each reaction, 4.0µL of genomic DNA were used at a final concentration of 2.5ng/µL; 2.5µL of 10x buffer (10mM Tris and 50mM KCl); 0.5µL of 50mM MgCl2 (Ludwig Biotec, Alvorada, Rio Grande do Sul, Brazil), 0.5µL of triphosphate deoxyribonucleotides (dNTPs; 2.5mM; (Ludwig Biotec, Alvorada, Rio Grande do Sul, Brazil); 0.5µL of Taq-Polymerase, (Ludwig Biotec, Alvorada, Rio Grande do Sul, Brazil), 5U/µL); 1.5µL of each forward and reverse oligonucleotide (10µM, IDT technologies); completing with Milli-Q water to a final volume of 25µL per reaction.

The PCR product in question was a 304pb fragment, subsequently digested with the restriction enzyme AvaI (New England Biolabs, Inc. Ipswich, Massachusetts, USA). Allele 1 (C) creates a new restriction site, and the 304pb fragment is cleaved into two of 190pb and 114pb. Allele 2 (T) is not cleaved by the enzyme, and thus, the polymorphism was divided into cleavage genotype, or homozygous ancestor (CC), heterozygous (CT), and non-cleavage genotype, or homozygous recessive (TT). To assemble the digestion system, the following were used: 10.0 µL of PCR; 2.0µL of 10x NEB4 buffer (Biolabs); 1 µL of AvaI enzyme (10U/µL), completing with Milli-Q water for a final volume of 20 µL per reaction. The system was held at 37°C for 3 hours. The digestion products were submitted to an electrophoretic run on a 3% agarose gel with 0.1% ethidium bromide at a power of 100W for 20 minutes.

To quantify the interleukin IL-1β in the patient's serum, the blood sample was collected in endotoxicin-free tubes and the analysis was performed using the Life Technologies sandwich immunoassay kit specific for human IL-1β, Human IL-1β. 1β ELISA Kit (catalog #KHC0011, lot #74788401A) as instructed by the manufacturer. Briefly, the sample was added to wells that have the primary antibody against the protein of interest (antigen) adsorbed to the bottom of the plate. Then, a specific antibody was added against the antigen and labeled with an enzyme (HRP – Horseradish Peroxidase) that reacts with a colorless substrate, producing a colored product proportional to the amount of protein of interest in the sample and capable of quantification at 450/550 nm. The sample was compared to a standard curve with known concentrations. Values greater than 2.08 pg/mL are considered high serum values. These serum levels were measured only once in the control group and in the case group, at admission to radiopharmaceutical treatment and seven days after treatment.

Adherence to the Hardy-Weinberg equilibrium for genotype frequency in controls was analyzed using the chi-square test with one degree of freedom. The genotype and allele frequencies of patients with papillary thyroid cancer who underwent radioiodine therapy were compared to the control group using the chi-square test in recessive and dominant models. The association of clinical characteristics for each genotype was analyzed using the chi-square test and a significance level of 5% was adopted. Odds ratio (OR) of allele and genotype frequencies were also calculated, with a confidence interval (CI) of 95%. The statistical program used was SPSS (version 20.0, SPSS Inc., Chicago, IL, USA). To compare the means of cytokine dosages, ANOVA or Student's t-test, or Pearson's correlation, were used, observing the assumptions of normality. To verify the other clinical characteristics and genotypes, the non-parametric Kruskall-Wallis H test was used.

Results

The genotype frequencies of the IL1B -511 polymorphism in healthy subjects were in Hardy-Weinberg equilibrium (P = 0.513). The genotypic distribution did not differ significantly between individuals with papillary thyroid cancer and healthy individuals (P = 0.651), with the number of individuals with the GG, GC and CC genotypes being 11, 13 and 2, respectively, in the CPT group, and 14, 11 and 1 in the control group. In addition, the evaluation between the C and T alleles was analyzed (P = 0.387; OR = 0.69; 95% CI = 0.29 – 1.61). It can be concluded that the presence of the rs16944 polymorphism of the IL-1B gene was not associated with susceptibility to papillary thyroid cancer (Table 1).

Table 1- Genotypic and allelic distributions of PTC carriers and controls. Federal District, 2022.

		Group					
		CPT		Control			
		N	%	N	%	P	OR (IC95%)
Genotypes	CC	11	42,3%	14	53,8%		
	CT	13	50,0%	11	42,3%	0,651	NA
	TT	02	7,7%	01	3,8%		
	Total	26	100,0%	26	100,0%		
Alelos	C	35	67,3	39	75,0		
	T	17	32,7	13	25,0	0,387	0,69 (0,29-1,61)
	Total	52	100,0	52	100,0		

NA: Not Applicable

Serum levels of IL-1β did not differ statistically between participants in the control group and patients with PTC before radiopharmaceutical treatment, however, serum levels of the cytokine increased three times more after radioiodine therapy (104.28 ± 32.25 pg/mL) compared to pre-treatment levels (15.15 ± 3.24 pg/mL) (P<0.001; Figure 1).

When carrying out the study of the difference in the mean levels of the cytokine in the different genotypes, it was possible to verify the statistical difference only in the serum level of IL-1β after radioiodine therapy, with the CC genotype associated with the highest mean production of the serum cytokine (Table 2).

Table 2- Serum levels of Il1-β according to genotype, in different study groups. Federal District, 2022.

		***IL1B* -511**												
		CC				**CT**				**TT**				
Group	IL-1 (pg/mL)	Average	Standard Deviation	CL lower 95,0% to medium	CL higher 95,0% to medium	Average	Standard Deviation	CL lower 95,0% to medium	CL higher 95,0% to medium	Average	Standard Deviation	CL lower 95,0% to medium	CL higher 95,0% to medium	P
Câncer	Antes	15,81	3,66	13,35	18,27	15,08	2,86	13,35	16,82	11,96	2,27	-8,44	32,35	0,313
	Depois	123,33 a	28,56	104,15	142,52	94,78 b	27,14	78,38	111,18	61,21 b	11,62	-43,2	165,62	0,008*
Controle		6,8	1,9	5,7	7,9	6,83	1,69	5,69	7,97	7,72				0,966

* P < 0,05 - Different letters denote statistical difference.

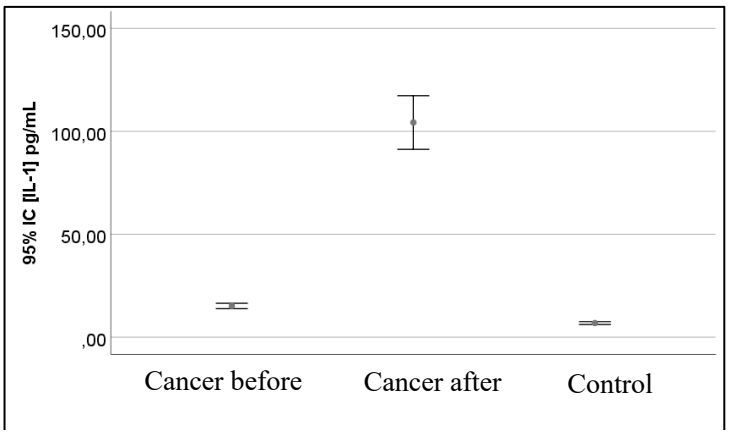

Figure 1- Serum levels of IL-1B in the different study groups. Federal District, 2022.

Therefore, the correlation analysis of the administered dose and the serum level of IL1-B (Table III), revealed independence between these variables, and only the serious levels of IL1-β of patients with PTC before and after treatment with CPT were correlated. the radiopharmaceutical, which corroborates the previous analysis. Thus, we can state that the increase in serum levels of IL-1β after treatment was not dose-dependent on the radiopharmaceutical.

Table 3 - Study of the correlation between the administered dose of the radiopharmaceutical and the serum levels of the cytokine. Federal District, 2022.

Correlations					
		Administered Dose (mCi)	**[IL-1] pg/mL control**	**[IL-1] pg/ before iodine therapy**	**[IL-1] pg/mL after Before iodine therapy**
Administered Dose (mCi)	Pearson Correlation	1	NA	-0,061	-0,092
	Folow. (2 ends)			0,766	0,656
	N	30		26	26
[IL-1] pg/mL control	Pearson Correlation	NA	1	-0,042	-0,068
	Folow. (2 ends)			0,838	0,743
	N		26	26	26

[IL-1] pg/ before iodotherapy	Pearson Correlation	-0,061	-0,042	1	,854**
	Folow. (2 ends)	0,766	0,838		0,000
	N	26	26	26	26
[IL-1] pg/mL after iodotherapy	Pearson Correlation	-0,092	-0,068	,854**	1
	Folow. (2 ends)	0,656	0,743	0,000	
	N	26	26	26	26

**. The correlation is significant at the 0.01 level (2 ends).
NA: Not applicable

Finally, other clinical characteristics of the patients were related to the genotype. Only the administered dose was statistically associated with the genotypic distribution (P<0.05), and there seems to be a tendency towards the presence of the T polymorphic allele and higher administered doses of the radiopharmaceutical (Tables 4 and 5).

Table 4 - Medians, median intervals and P-values of thyroglobulin, TSH and BMI measurements in patients with PTC according to genotype. Federal District, 2022.

	[Thyroglobulin] ng/Ml			**[TSH] µUI/mL**			**IMC (kg m-2)**		
IL1B - 511	CL lower than 95.0% for median	Median	CL higher than 95.0% for median	CL lower than 95.0% for median	Median	CL higher than 95.0% for median	CL lower than 95.0% for median	Median	CL higher than 95.0% for median
CC	0,77	1,8	9	14,27	77,28	117,23	24,34	30,47	38,22
CT	1,06	2,98	8,09	7,46	65,91	130,07	23,24	24,62	31,61
TT	31,99	113,5	195	17,65	69,33	121	23,67	24,95	26,22
P-Valor		0,118			0,935			0,223	

Table 5- Study of the association between antithyroglobulin distribution, sex and radiopharmaceutical dose administered in patients with PTC according to genotype. Federal District, 2022.

***IL1B* -511**	**Antithyroglobulin (UI/mL)**				**Sex**				**Administered dose (mCi)**									
	<20		**>20**		**Female**		**Masculine**		**50**		**100**		**150**		**200**		**250**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
CC	6	40,0 %	3	75,0%	7	43,8%	4	40,0%	1	100,0%	4	50,0%	6	42,9%	0	0,0%	0	0,0%
CT	8	53,3 %	1	25,0%	7	43,8%	6	60,0%	0	0,0%	4	50,0%	8	57,1%	1	50,0%	0	0,0%
TT	1	6,7%	0	0,0%	2	12,5%	0	0,0%	0	0,0%	0	0,0%	0	0,0%	1	50,0%	1	100,0 %
P-valor		0,445				0,451								0,008*				

Discussion

In the present study, it was found that the presence of the IL1B -511 polymorphism was not associated with susceptibility to papillary thyroid carcinoma.

The evaluation of the -511 polymorphism for cancer susceptibility is quite controversial in the literature, and depends on the type of cancer evaluated. A meta-analysis performed by Xu et al[20] pointed out that the dominant model for this polymorphism is not associated with susceptibility to some types of cancer. However, the recessive model is associated with cervical carcinoma and is a protective factor for hepatocellular carcinoma. Furthermore, the heterozygous genotype is a risk factor for specific subtypes of gastric carcinoma. On the other hand, Yencilek et al[21] determined that the heterozygous genotype decreased the risk for prostatic carcinoma.

In contrast, other IL1B polymorphisms were evaluated for CPT in a Korean population. The results found suggested that a polymorphism in the promoter region (-31) is a protective factor in the recessive model, and several SNPs in intron regions constituted protective factors (rs3136558 – codominant and dominant model), risk factors (rs1143633, rs1143643, rs1143630 in the codominant and dominant models) and rs3136558 was considered a risk factor with the recessive allele.[22]

The present study also made it possible to verify an increase in cytokines after radioiodine therapy ($P<0.001$), where such a difference was statistically associated with the CC genotype.

A study carried out by Langmia et al.23 identified that the plasmatic levels of IL-1B did not differ according to the genotypic distribution of IL1B. On the other hand, a study carried out in patients with rheumatoid arthritis in North India revealed that IL1-B levels differed according to genotypes, with the CC genotype being associated with lower levels of the cytokine,[24] evidence that was the opposite of what was found in this study.

The increase in cytokine expression after exposure to radiation has also been detected by other studies. In this sense, it was observed that radiation treatment was inducing the production of IL1-B cytokines in mice submitted to X-radiation treatment, as described by Hong et al.[25]

Furthermore, as IL-1B production has a positive effect on tumor growth, Perrone et al.[26] suggest, after observing the effect of radiotherapy dose on mice, that a therapy to block cytokine production would be important for adequate response to treatment by the patient. It is also noteworthy that the increase in pro-inflammatory cytokines is associated with depressive behaviors, as reviewed by Miller, Maletic and Raison,[27] which impacts the quality of life of patients undergoing treatment with radiopharmaceuticals.

Finally, variations in thyroid function are identified in normal individuals, and are evidenced by small changes in serum levels of thyroid hormones and TSH compared to other individuals. Genetic and environmental factors can cause such alterations.[28] Among the environmental factors, alterations in the inflammatory process stand out in association with changes in thyroid function. For example, in patients with glomerulonephritis, laboratory signs of hypothyroidism of different degrees of severity were identified, accompanied by

increased levels of production of pro-inflammatory cytokines IL-1b and IL-4, related to activity with a humoral link of adaptive immunity .29 However, in the present study, no association was observed between the IL1B -511 polymorphism and hormone tests.

Conclusion

The IL1B -511 polymorphism was not associated with papillary thyroid cancer in the Brazilian population studied, nor with basal serum levels of the cytokine, both in controls and in patients with PTC. Despite this, it was possible to identify an increase in cytokine levels after treatment with the radiopharmaceutical sodium iodide. Evaluating genetic factors and determining circulating levels of cytokines such as IL-1β can serve as a promising non-invasive method to differentiate benign from malignant thyroid conditions, in addition to assisting in the treatment and reduction in mortality rates.

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Correspondent Author
Izabel Cristina Rodrigues da Silva.
University Campus, s/n, Centro Metropolitano.
ZIP: 72220-275. Brasília, Distrito Federal, Brazil.
belbiomedica@gmail.com