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Review article

Thyroid cancer in Ecuador: A genetic variants review and a cross-sectional population-based analysis before and after COVID-19 pandemic

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ABSTRACT

Objectives: The purpose of this study is to describe the genetic variants present in the Ecuadorian population and the incidence and mortality patterns of thyroid cancer in Ecuador from 2016 to 2021.

Methods: The present research constitutes a nationwide cross-sectional study encompassing all reported cases of thyroid cancer (C-73) in Ecuador from 2016 to 2021. Incidence rates were calculated based on the annual population at risk, considering factors such as ethnicity, sex, age group, and the geographic location of the incidence. All data was collected from the Hospital Discharge Statistics and the Statistical Registry of General Deaths Databases.

Results: Between 2016 and 2021, a total of 20,297 hospital admissions and 921 deaths attributed to thyroid cancer were reported in Ecuador. The incidence of thyroid cancer remained relatively stable from 2016 to 2019. However, there was a notable decrease in 2020, followed by an increase in 2021. Notably, thyroid cancer prevalence rates were found to be higher in highlands regions. Moreover, two genetic variants, the $BRAF^{V600E}$ and KIT^{L678F}, have been identified in the Ecuadorian population. It is noteworthy that women exhibited a higher susceptibility to thyroid cancer, being five times more likely than men to develop this condition.

Conclusion: Ecuador exhibits one of the highest global incidences of thyroid cancer. Consequently, describing the genetic variants and epidemiological characteristics of thyroid cancer is imperative for enhancing healthcare access and formulating evidence-based public health policies. This research contributes towards a comprehensive understanding of thyroid cancer in the Ecuadorian context, aiming to improve targeted interventions and health outcomes.

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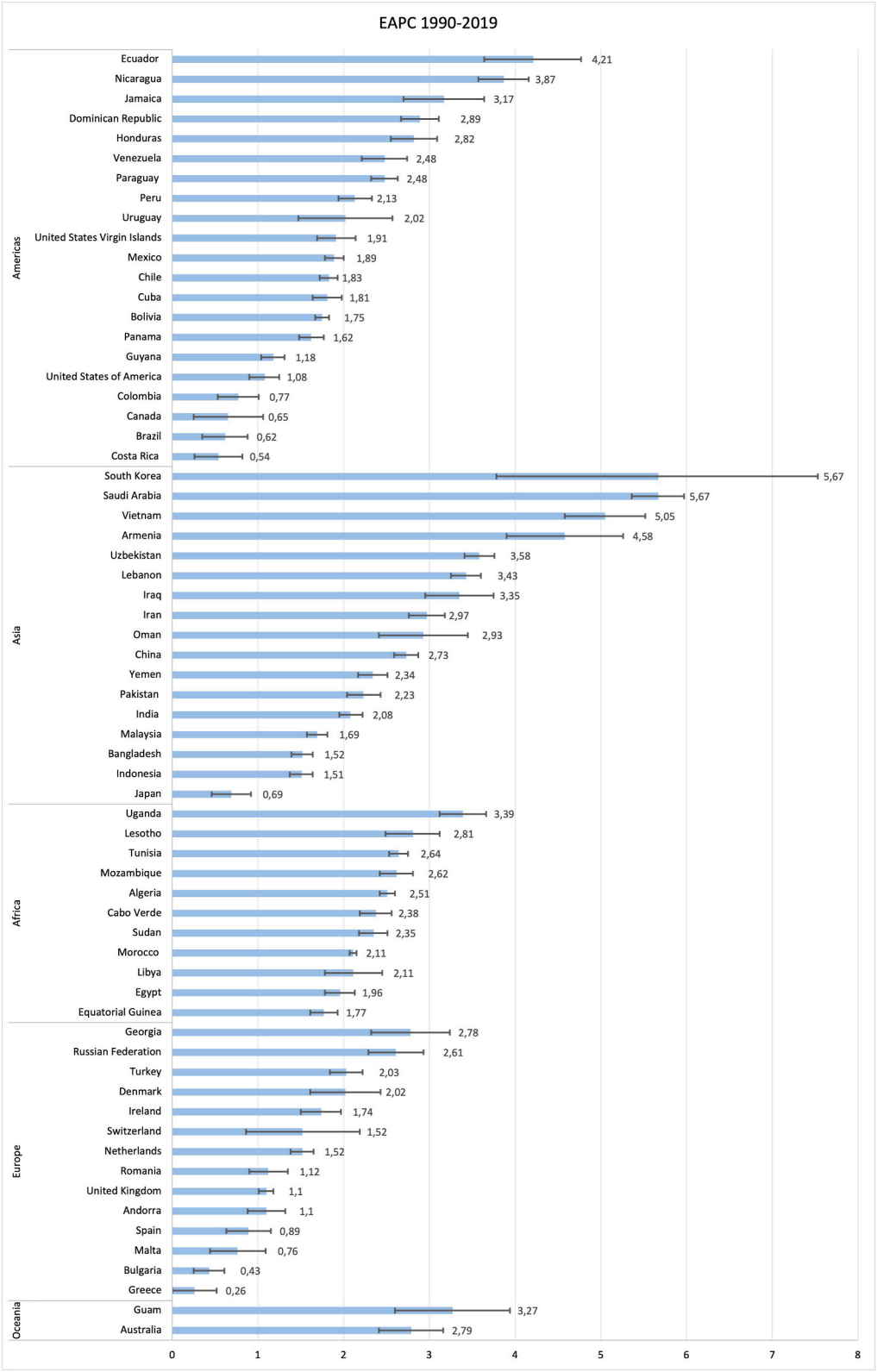

Fig. 1. Estimated annual percentage changes (EAPCs) from 1990 to 2019.

1. Introduction

Thyroid cancer (TC) is the most common endocrine neoplasia, with its incidence increasing every year [1]. Ecuador exhibits the highest TC incidence among Latin American countries and one of the highest in the world [2]. Deng et al. (2020) and Bao et al. (2021) investigated the incidence of TC and its temporal trends in 204 countries between 1990 and 2019. Their findings revealed that Ecuador has the highest estimated annual percentage change (EAPC) in South America and is among the top five globally (Fig. 1) [3,4].

In 2012, Ecuador exhibited the highest TC incidence rate in South America and the second highest in the world (38.7 for women and 6.8 for men per 100,000 inhabitants) [5]. However, by 2017 and 2019, the incidence rates of TC in Ecuador declined to 5.29 (4.48–6.23) and 4.62 (3.43–6.15) per 100,000 individuals, respectively. Despite this reduction, these rates remained the highest among South American countries, with other countries in the region reporting at least 1 case less per 100,000 inhabitants during the same years [3,4].

Additionally, data from the International Agency for Research on Cancer revealed that in 2020, TC ranked as the fifth most diagnosed malignant tumor in Ecuador, accounting for 1685 cases, and the sixth in South America, totaling 47,943 [6,7]. It is estimated that by 2040, the number of TC cases increase to 2100 in women and 350 in men [8].

TC is classified according to its histopathological characteristics into differentiated TC (DTC), poorly differentiated TC (PDTC), and anaplastic TC (ATC) [9]. DTC comprises over 90 % of the cases and further divides into two subtypes: papillary TC (PTC) and follicular TC (FTC) [10]. FTC and PTC are high-risk carcinomas with high recurrence probability; hence, they must be diagnosed early to initiate adequate treatment [9,11].

PDTC and ATC represent approximately 5 % of TC cases and are characterized by more aggressive behavior and lower survival rates [9]. The remaining 5 % of cases correspond to medullary TC (MTC), which derives from parafollicular C cells and has been reported to be inherited in an autosomal dominant manner in 25 % of cases [12].

The increase in TC incidence shows geographic disparities. Some countries have reported a notably high and increasing incidence, while others describe a relatively low incidence with minimal growth. These inequalities may stem from differences in healthcare systems, access to care, and cancer screening practices [13–15].

The substitution from valine (V) to glutamic acid (E) at codon 600 of the BRAF gene ($BRAF^{V600E}$) is the most reported mutation in PTC [9,16]. BRAF mutations can lead to the activation of the BRAF kinase in the MAPK pathway, representing the initial event in the oncogenesis and progression of PTC [9]. An association between $BRAF^{V600E}$ variant presence and worse prognosis, extrathyroidal extension, and lymph node metastasis has also been established [17].

The objective of this study is to elucidate the genetic variants present in the Ecuadorian population, alongside exploring the incidence and mortality patterns of TC in Ecuador from 2016 to 2021.

2. Methods

2.1. Study population

The present manuscript describes a nationwide cross-sectional study encompassing all reported cases of TC (C-73 code) in Ecuador over a six-year period (2016–2021). All data was obtained from the Open Data Bank of the National Institute of Censuses and Statistics (INEC).

2.2. Data sources

Data from the last six years was collected from the Hospital Discharge Statistics and the Statistical Registry of General Deaths Databases. The website https://aplicaciones3.ecuadorencifras.gob.ec/BIINEC-war/index.xhtml contains the annual records.

This study did not involve human participants. All the data comes from secondary, non-identifiable public records obtained from the Hospital Discharge Statistics and the Statistical Registry of General Deaths Databases, accessible on the Open Data Bank website of the National Institute of Statistics and Census of Ecuador. Therefore, institutional review board assessment was not necessary, in accordance with the Organic Law on Transparency and Access to Public Information of Ecuador.

TC statistics (C-73) were analyzed by year at canton and province levels. Data were categorized by place of residence, the place where treatment was provided, sex, age, and ethnic origin.

2.3. Data analysis

The incidence, prevalence, and mortality rates were age-standardized using the 2010 national population census as a reference. Rates were calculated using the annual population at risk, considering factors such as ethnicity, sex, age group, and the geographic location of the incidence. Statistical analyses were conducted using the IBM SPSS statistics v24.0. Spatial analysis was performed using the software QGIS v2.8.

3. Results

3.1. Genetic variants

Only two genetic variants have been identified in the Ecuadorian population. The first variant is a heterozygous mutation in the BRAF gene, involving an adenine-to-thymine change at position 1799. This mutation causes an amino acid change from Valine to Glutamic acid at position 600 ($BRAF^{V600E}$). Pazmiño et al. (2023) analyzed the exon 15 of the BRAF oncogene using paraffin-embedded tissue samples from 193 patients through Sanger sequencing. They identified the mutation $BRAF^{V600E}$ in 146 cases, accounting for 75.6 % of the samples [18].

The second genetic variant is a heterozygous mutation in the KIT gene, involving a thymine-to-cytosine at position 2032. This mutation induces an amino acid change from Leucine to Phenylalanine at position 678 (KIT^{L678F}). Cadena-Ullauri et al. (2023) analyzed a thyroid tissue sample from a patient with PTC by next-generation sequencing. Findings revealed the presence of both mutations $BRAF^{V600E}$ and KIT^{L678F} mutations in the sample [19].

3.2. Statistics of thyroid cancer

Between 2016 and 2021, Ecuador recorded 20,297 TC cases. The mean age at diagnosis was 49 years (±15 years), with 83 % of cases occurring in women. Predominantly, patients were attended in urban areas (96 %), and received treated through various healthcare systems: public health care system (42 %), private for-profit health care system (45 %), and private non-profit health care system (13 %). TC was more frequently reported among individuals of mestizos ethnicity, constituting 75.5 % of the cases.

3.3. Incidence, prevalence, and mortality

The annual incidence was relatively stable from 2016 to 2019. The annual average prevalence was lower in men, with 7.2 ± 0.33 cases per 100,000 inhabitants, compared to women, in which case it was 35.97 ± 1.31 cases per 100,000. In 2020, the incidence decreased to 14 cases per 100,000 individuals, followed by an increase in 2021 to 19 cases per 100,000. The female-to-male incidence ratio was approximately 5:1 (Fig. 2).

The prevalence rates exhibit a high geographical variation. Upon provincial analyses, the prevalence rate from 2016 to 2021 ranges from 27 cases per 100,000 inhabitants in Orellana to 277 cases per 100,000 in Chimborazo (Supplementary Fig. 1).

Analyzing by cantons, the highest prevalence rate was observed in Guachapala, Azuay, with 598.06 cases per 100,000 inhabitants, followed by Riobamba, Chimborazo, with 476.80 cases per 100,000. On the other hand, the lowest prevalence rate was 2.18 cases per 100,000 individuals in Eloy Alfaro, Esmeraldas. The highlands region exhibited a prevalence rate of 199 per 100,000 individuals, followed by the Amazon region with 64 per 100,000 and the coastal region (including the Galapagos Islands) with 60 per 100,000 (Fig. 3).

TC mortality rate was 0.58 ± 0.12 deaths in men and 1.22 ± 0.14 in women per 100,000 inhabitants. The female-to-male mortality ratio was approximately 2:1 (Fig. 4).

When analyzing by age groups, the mortality rate in infants, children, and adolescents (0–19 years) was 0.01 per 100,000 inhabitants. This rate slightly increases to 0.18 per 100,000 in young adults (20–39 years). The highest mortality rate was 1.26 per 100,000 in adults aged 80 and older (Fig. 5).

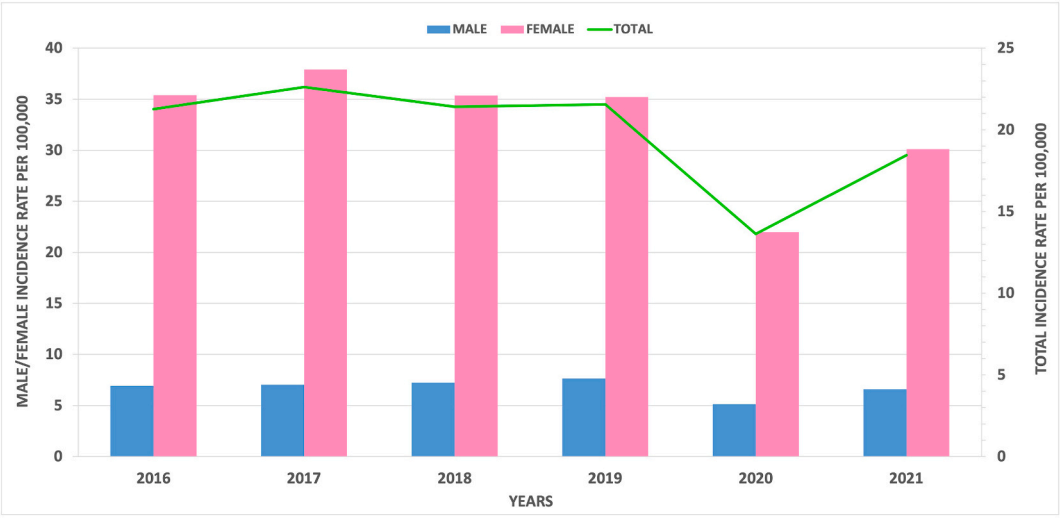

Fig. 2. Male, female, and total annual incidence rates for thyroid cancer in Ecuador from 2016 to 2021.

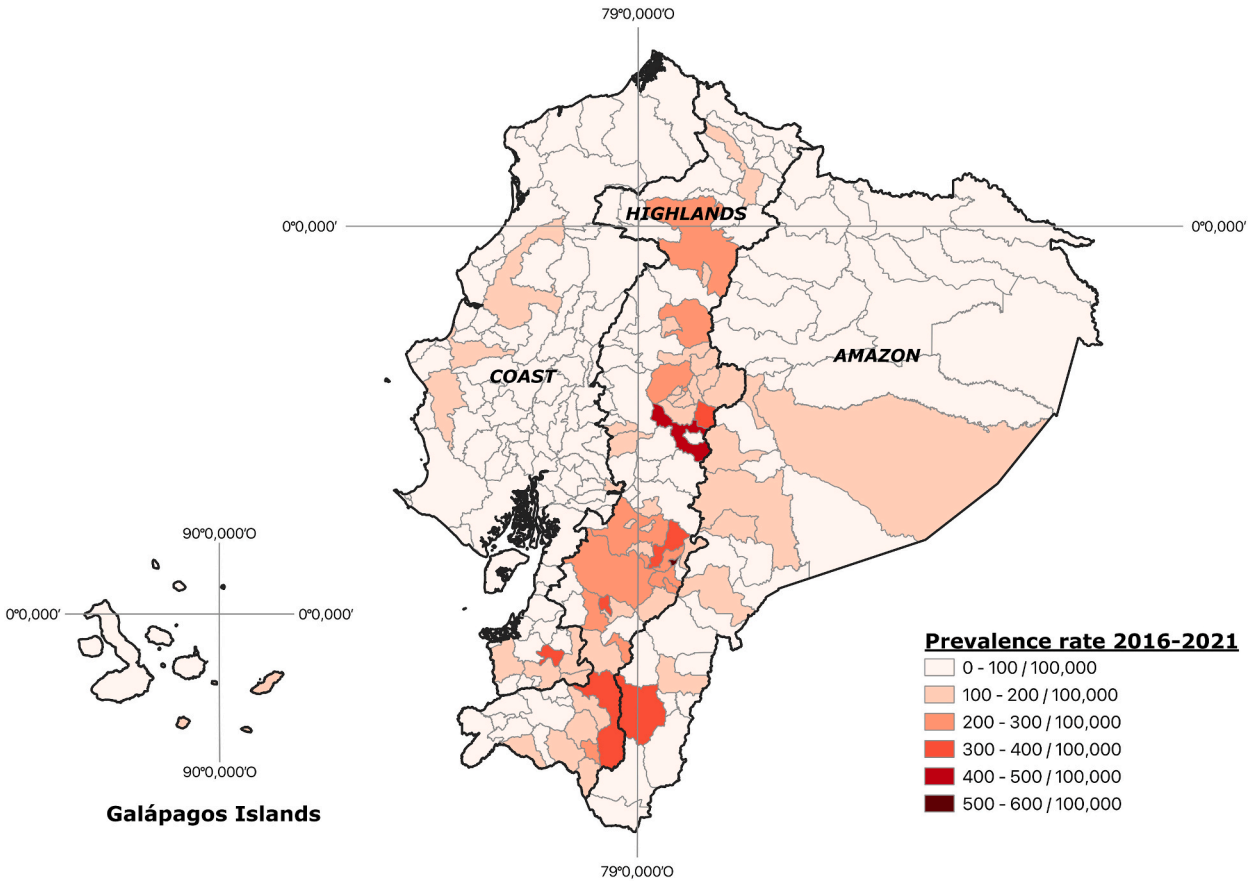

Fig. 3. Prevalence rates of thyroid cancer in Ecuador according to cantons, from 2016 to 2021.

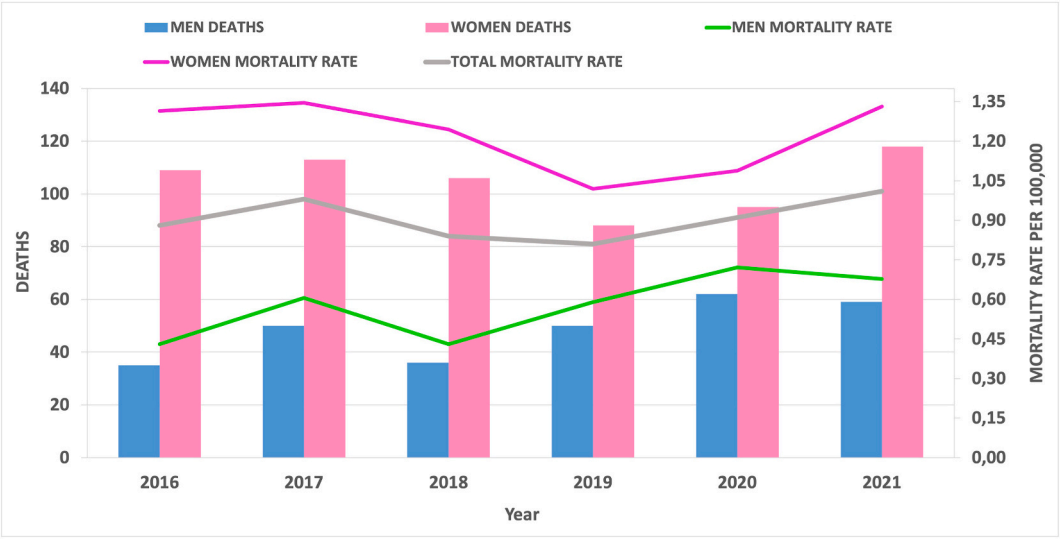

Fig. 4. Annual deaths and mortality rate per 100,000 individuals of thyroid cancer in Ecuador from 2016 to 2021 in men and women.

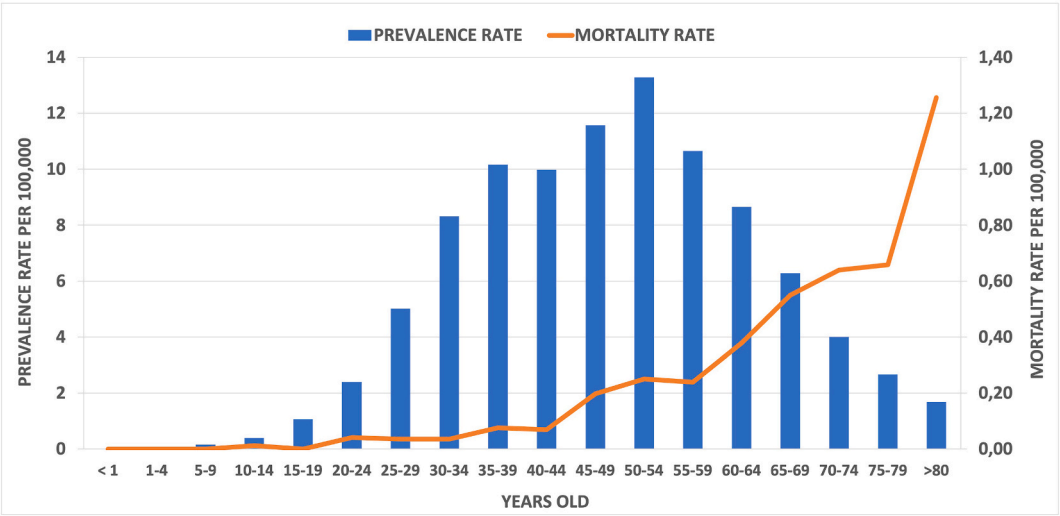

Fig. 5. Prevalence rate and mortality rate per 100,000 inhabitants of thyroid cancer in Ecuador by age group from 2016 to 2021.

3.4. Trends

Between 2016 and 2019, the incidence of TC remained relatively stable at approximately 22 cases per 100,000 inhabitants. In 2020, the incidence decreased to 14 cases per 100,000 inhabitants, rising again in 2021 to 19 cases per 100,000. Gender-wise analysis revealed a relatively constant incidence rate of approximately 36 cases per 100,000 women per year from 2016 to 2019, compared to approximately 7 cases per 100,000 men during the same period. Between 2020 and 2021, the incidence increased from 5.13 to 6.61 cases per 100,000 men, and from 21.99 to 30.11 cases per 100,000 women (Fig. 6). Over the period of 2016–2021, the annual average

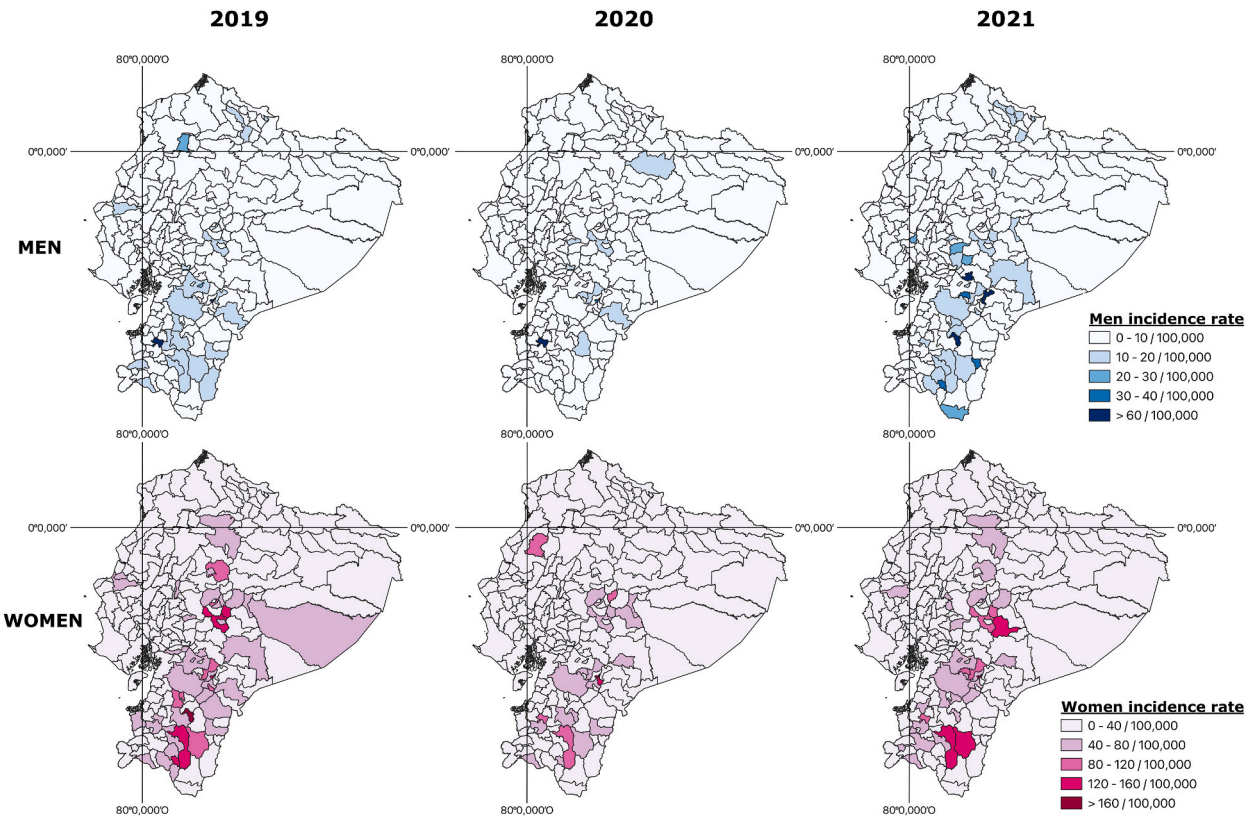

Fig. 6. Incidence rate per 100,000 thyroid cancer cases in Ecuador in 2016, 2020 and 2021.

mortality rate was 0,91 ± 0,08 deaths per 100,000 inhabitants.

4. Discussion

In Ecuador and in several other countries worldwide, the incidence of PTC has increased in the last three decades [15,20–23]. TC has now become the fifth most diagnosed cancer in the Ecuadorian population [23]. Certainly, cancer represents a global challenge, and its prevalence is expected to increase in the coming decades. Projections indicate a substantial increase in the cancer burden within Latin America, from 1.5 million new cases to over 2.4 million by 2040. Specifically, the estimates indicated a 4.3 % increase in new cases of TC by 2040 [24].

The increment in TC incidence could be attributed to the overdiagnosis of small incidental tumors [25]. Nevertheless, some studies indicate an increase in larger and more aggressive tumors, suggesting the involvement of other factors influencing PTC incidence [26,27]. Several studies suggest that TC incidences are different among populations. Zheng et al. (2022) reported that African-American individuals had a lower probability of TC in thyroid nodules. They also noted that, irrespective of tumor size, TC in African-American patients was less likely to metastasize to the lymph nodes [28,29]. In contrast, Finlayson et al. (2014) identified a higher incidence of TC in most ethnic minority groups in England [30]. Thus, population-specific factors, such as American Indian ancestry, which could influence other cancer patterns, may contribute to an elevated risk of PTC in the Ecuadorian population [31,32]. The higher prevalence of TC among the mestizo Ecuadorian population can be attributed to their status as the largest ethnic group in the country.

TC incidence and mortality in Ecuador surpass those in other Latin American countries, ranking among the highest globally [33,34]. We hypothesize that the higher incidence of TC in Ecuador is due to the implementation of new radiological technologies, which facilitates early detection of a higher number of small tumors, typically clinically undetectable [35]. Over the past two decades, Ecuador has made significant strides in enhancing both public and private healthcare, ensuring increased and improved healthcare access for its population. This progress is likely be the main reason related to overdiagnosis [36,37].

Our study reveals that the incidence and mortality rates of TC have remained relatively stable since 2016, at 22 cases and 1 death per 100,000 inhabitants, respectively. This trend diverges from the findings reported by Salazar-Vega et al. (2019), who documented a rise in the annual incidence from 3 cases in 2001 to 22 cases in 2016 per 100,000 inhabitants [15]. In 2020, amidst the COVID-19 pandemic, the incidence dropped to 14 cases per 100,000. However, in 2021, it increased again to 19 cases per 100,000. The impact of the pandemic on healthcare services was significant. Despite the policies implemented to reduce the number of infections, the SARS-CoV-2 virus collapsed the national health system, placing Ecuador among the most affected countries in Latin America. Ecuador's largest hospitals had to transition from general healthcare centers to COVID-19-specific facilities, prioritizing patients with respiratory conditions. Unfortunately, this transition left many patients without specialized care, who had to wait for the progressive reopening of medical specialties at healthcare centers [38].

Our research shows that most patients with TC reside in the Ecuadorian highlands, with higher prevalence rates observed in the Andean regions (average altitude 2500 masl). Notably, between 2016 and 2021, the provinces of Chimborazo, Azuay, and Loja had the highest prevalence rates. Guachapala in Azuay province was the canton with the highest prevalence rate at 598.06 cases per 100,000 inhabitants. However, given its small population of approximately 3400 inhabitants, its rates statistics are not representative. The second-highest prevalence rate was observed in Riobamba (476.80 cases per 100,000 individuals).

Furthermore, several studies have suggested that an active volcanic environment can be a risk factor for developing thyroid cancer [39,40]. Additionally, Vigneri et al. (2017) established that environmental metal pollution, even at low levels, can contribute to the propagation of altered thyroid cells, potentially increasing the risk of thyroid cancer [41].

Upon analyzing the incidence and mortality across age groups, we observed that TC has a relatively low impact on children, adolescents, and older adults. However, mortality rates increased from 4.37 % in individuals aged 60–64 to 74.46 % in both men and women over 80 years. This increase in mortality could be due to the higher prevalence of comorbidities within this age range.

Our results affirm that Ecuador exhibits the highest incidence rates in Latin America, yet there is a scarcity of studies addressing the epidemiology of this neoplasia. Limited research has been conducted, with only a few studies reporting significant variations in TC incidence over the last two decades [2,15,20–22,25,42,43]. Notably, the number of cases increased nearly twentyfold from 2001 to 2021 [15]. While the epidemiological reports are limited, the genetic investigations are even scarcer. A single study from Pazmiño et al. (2023) revealed a $BRAF^{V600E}$ mutation in 146 of 193 (75,6 %) PTC patients from the northern Ecuadorian Andes treated at Hospital Eugenio Espejo in Quito, Ecuador [43]. This study corroborates the high prevalence of the $BRAF^{V600E}$ variant in Ecuadorian patients with PTC, aligning with global trends [44,45].

Despite $BRAF^{V600E}$ being the most prevalent mutation, our research group identified a novel variant in the KIT gene (KIT^{L678F}) in an Ecuadorian woman with Native American ancestry [2], further diversifying the genetic landscape associated with PTC in the Ecuadorian population.

Genetic variations, encompassing both single nucleotide polymorphisms (SNPs) and point mutations, have a substantial impact on various cellular pathways such as cell apoptosis, DNA repair mechanisms, folate metabolism, and inflammation. Germline mutations in key genes such as BRAF, RAS, RET, TERT, MET, BAX, TP53, XRCC1, VDR, SPARC, SPP1, MMP-9, NRG1, FOXE1, PAX8/PPAR-γ, and NTRK profoundly influence the susceptibility to TC [46,47].

The significance of mitogen-activated protein kinase (MAPK) pathway activation is well-established, primarily attributed to the role of point mutations of the BRAF and RAS genes, as well as RET/PTC rearrangements, in the molecular pathogenesis of PTC [48,49]. In contrast, the precise role of KIT in cancer is remains unknown, with many investigations presenting discrepancies according to the type of tumor. Some studies show that KIT is highly expressed or mutated in small-cell lung cancer, leukemia cells, colon cancer, and neuroblastoma. Conversely, other studies suggest loss of KIT expression in breast cancer and melanoma [50]. Notably, during the

transformation from normal thyroid epithelium to papillary carcinoma, a downregulation of KIT expression has been observed, suggesting a potential role in the differentiation of thyroid tissue [50,51].

Notably, specific variations within the RET and MET genes exhibit a strong correlation with a risk of thyroid cancer, especially in papillary thyroid cancer. Genetic variants in BAX, TP53, and HOTAIR significantly impact cell apoptosis and DNA repair mechanisms, thereby contributing to the development of thyroid cancer. Moreover, SNPs in genes associated with folate metabolism and inflammatory cytokines distinctly influence the risk of thyroid cancer [46].

Moreover, epigenetic changes, such as DNA methylation, chromatin remodeling, histone modification, and non-coding RNA regulation, play a key role in the development and risk of thyroid cancer. Notably, PTC demonstrates lower DNA methylation frequencies in contrast to FTC, which is characterized by marked hypermethylation/hypomethylation patterns. Non-coding RNAs, including miRNA, lncRNA, and circRNA, serve as crucial regulators, influencing oncogenes, tumor suppressors, and pivotal pathways in thyroid cancer. Among these, miR-34 and miR-221 have been extensively studied in both PTC and FTC, and they are recognized as key regulators of thyroid carcinogenesis in well-differentiated tumors [52].

Comprehending these genetic variations and epigenetics factors is crucial for predicting an individual's risk of thyroid cancer, determining prognosis, and customizing treatments for each patient. Further comprehensive research is essential to delve deeper into these genetic and epigenetic associations across diverse populations, thereby enhancing the understanding of how genetic factors intricately influence thyroid cancer.

5. Limitations

The main limitation of the study is associated with the use of the Hospital Discharge Statistics Database, which is not specifically designed to discriminate between the multiple instances that the same patient enters and leaves a hospital. Additionally, it may not capture thyroid cancer cases that do not require hospitalization, leading to a potential risk of case duplication.

6. Conclusion

This report highlights that the predominant genetic variant associated with TC in the Ecuadorian population is the $BRAF^{V600E}$. Furthermore, our findings indicate a higher TC incidence in women and in regions with high altitudes. The description of genetic variants and their correlation with epidemiological factors is essential for enhancing health access and promoting evidence-based public health policies. Further analyses are needed to identify risk factors contributing to an elevated susceptibility to TC, especially those associated with altitude and environmental composition.

Ethics approval and consent to participate

This study did not involve human participants. All the data comes from secondary unidentifiable public records. Therefore, institutional review board assessment was not necessary per the Organic Law on Transparency and Access to Public Information of Ecuador.

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Data availability

The Hospital Discharge Statistics and the Statistical Registry of General Deaths Databases are available at the Open Data Bank website of the National Institute of Statistic and Census of Ecuador: https://aplicaciones3.ecuadorencifras.gob.ec/BIINEC-war/index.xhtml.

CRediT authorship contribution statement

Elius Paz-Cruz: Conceptualization, Methodology, Writing – review & editing. **Santiago Cadena-Ullauri**: Methodology, Writing – review & editing. **Patricia Guevara-Ramírez**: Methodology. **Viviana Ruiz-Pozo**: Methodology. **Rafael Tamayo Trujillo**: Methodology. **Daniel Simancas-Racines**: Methodology. **Ana Karina Zambrano**: Conceptualization, Methodology, Writing – review & editing, Supervision, Project administration, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e23964.

References

[1] L. Santarpia, J.N. Myers, S.I. Sherman, F. Trimarchi, G.L. Clayman, A.K. El-Naggar, Genetic alterations in the Ras/Raf/mitogen-activated protein kinase and phosphatidylinositol 3-kinase/Akt signaling pathways in the follicular variant of papillary thyroid carcinoma, Cancer 116 (12) (2010) 2974–2983, https://doi.org/10.1002/cncr.25061.

[2] S. Cadena-Ullauri, E. Paz-Cruz, R. Tamayo-Trujillo, et al., Identification of KIT and BRAF mutations in thyroid tissue using next-generation sequencing in an Ecuadorian patient: a case report, Front. Oncol. 12 (2023), https://doi.org/10.3389/FONC.2022.1101530/FULL.

[3] Y. Deng, H. Li, M. Wang, et al., Global burden of thyroid cancer from 1990 to 2017, JAMA Netw. Open 3 (6) (2020), https://doi.org/10.1001/JAMANETWORKOPEN.2020.8759.

[4] W.Q. Bao, H. Zi, Q.Q. Yuan, L.Y. Li, T. Deng, Global burden of thyroid cancer and its attributable risk factors in 204 countries and territories from 1990 to 2019, Thorac Cancer 12 (18) (2021) 2494, https://doi.org/10.1111/1759-7714.14099.

[5] M. Ervik, F. Lam, M. Laversanne, J. Ferlay, F. Bray, Global Cancer Observatory: Cancer over Time, International Agency for Research on Cancer. Published, 2021. https://gco.iarc.fr/overtime. (Accessed 15 November 2023).

[6] J. Ferlay, M. Colombet, I. Soerjomataram, et al., Cancer statistics for the year 2020: an overview, Int. J. Cancer 149 (4) (2021) 778–789, https://doi.org/10.1002/IJC.33588.

[7] H. Sung, J. Ferlay, R.L. Siegel, et al., Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, CA Cancer J Clin 71 (3) (2021) 209–249, https://doi.org/10.3322/CAAC.21660.

[8] J. Ferlay, M. Laversanne, M. Ervik, et al., Global Cancer Observatory: Cancer Tomorrow, International Agency for Research on Cancer. Published, 2020. https://gco.iarc.fr/tomorrow. (Accessed 15 November 2023).

[9] C. Nylén, R. Mechera, I. Maréchal-Ross, et al., Molecular Markers Guiding thyroid cancer Management, Cancers 12 (8) (2020) 1–26, https://doi.org/10.3390/CANCERS12082164.

[10] J.P. Brito, I.D. Hay, Management of papillary thyroid Microcarcinoma, Endocrinol Metab Clin North Am 48 (1) (2019) 199–213, https://doi.org/10.1016/J.ECL.2018.10.006.

[11] A. Prete, P. Borges de Souza, S. Censi, M. Muzza, N. Nucci, M. Sponziello, Update on Fundamental mechanisms of thyroid cancer, Front. Endocrinol. 11 (2020) 102, https://doi.org/10.3389/FENDO.2020.00102.

[12] H. Duan, X. Liu, X. Ren, H. Zhang, H. Wu, Z. Liang, Mutation profiles of follicular thyroid tumors by targeted sequencing, Diagn. Pathol. 14 (1) (2019), https://doi.org/10.1186/S13000-019-0817-1.

[13] H. Lim, S.S. Devesa, J.A. Sosa, D. Check, C.M. Kitahara, Trends in thyroid cancer incidence and mortality in the United States, 1974-2013, JAMA 317 (13) (2017) 1338–1348, https://doi.org/10.1001/JAMA.2017.2719.

[14] S. Park, C.M. Oh, H. Cho, et al., Association between screening and the thyroid cancer "epidemic" in South Korea: evidence from a nationwide study, BMJ 355 (2016), https://doi.org/10.1136/BMJ.I5745.

[15] J. Salazar-Vega, E. Ortiz-Prado, P. Solis-Pazmino, et al., Thyroid Cancer in Ecuador, a 16 years population-based analysis (2001–2016), BMC Cancer 19 (1) (2019), https://doi.org/10.1186/S12885-019-5485-8.

[16] C. Romei, R. Elisei, A narrative review of genetic alterations in primary thyroid epithelial cancer, Int. J. Mol. Sci. 22 (4) (2021) 1–16, https://doi.org/10.3390/IJMS22041726.

[17] J.A. Silver, M. Bogatchenko, M. Pusztaszeri, et al., BRAFV600E mutation is associated with aggressive features in papillary thyroid carcinomas $\leq$ 1.5 cm, Journal of Otolaryngology - Head & Neck Surgery (1) (2021) 50, https://doi.org/10.1186/S40463-021-00543-9.

[18] A.P.S. Pazmiño, T. Cardenas, J. Cucalon, et al., SAT516 impact of the braf V600E gene mutation in patients with papillary thyroid cancer from northern Ecuadorian Andes, J Endocr Soc 7 (Suppl 1) (2023), https://doi.org/10.1210/JENDSO/BVAD114.1988.

[19] S. Cadena-Ullauri, E. Paz-Cruz, R. Tamayo-Trujillo, et al., Identification of KIT and BRAF mutations in thyroid tissue using next-generation sequencing in an Ecuadorian patient: a case report, Front. Oncol. 12 (2023), https://doi.org/10.3389/fonc.2022.1101530.

[20] F.C. Cordero, P.C. Ayala, J.Y. Maldonado, W.T. Montenegro, Trends in cancer incidence and mortality over three decades in Quito-Ecuador, Colomb. Méd. 49 (1) (2018) 35–41, https://doi.org/10.25100/CM.V49I1.3785.

[21] E. López Gavilanez, N. Bautista Litardo, M. Navarro Chávez, M. Hernández Bonilla, A. Segale Bajaña, Thyroid cancer in Ecuador, BMC Cancer 20 (1) (2020), https://doi.org/10.1186/S12885-020-07137-0.

[22] L. Pacheco-Ojeda, A. Martínez-Jaramillo, H. Romo-Castillo, M. Mario Montalvo-Burbano, Differentiated thyroid cancer clinical trends in Quito, Ecuador, International Journal of Medical and Surgical Sciences 8 (2) (2021) 1–10, https://doi.org/10.32457/IJMSS.V8I2.1347.

[23] M. Ervik, F. Lam, M. Laversanne, J. Ferlay, F. Bray, Global Cancer Observatory: Cancer over Time, International Agency for Research on Cancer. Published, 2021. https://gco.iarc.fr/overtime. (Accessed 22 March 2023).

[24] M. Piñeros, M. Laversanne, E. Barrios, et al., An updated profile of the cancer burden, patterns and trends in Latin America and the Caribbean, The Lancet Regional Health - Americas 13 (2022), 100294, https://doi.org/10.1016/j.

[25] P. Solis-Pazmino, J. Salazar-Vega, E. Lincango-Naranjo, et al., Thyroid cancer overdiagnosis and overtreatment: a cross- sectional study at a thyroid cancer referral center in Ecuador, BMC Cancer 21 (1) (2021) 1–10, https://doi.org/10.1186/S12885-020-07735-Y/TABLES/5.

[26] R. Liu, J. Bishop, G. Zhu, T. Zhang, P.W. Ladenson, M. Xing, Mortality risk stratification by combining BRAF V600E and TERT promoter mutations in papillary thyroid cancer: genetic duet of BRAF and TERT promoter mutations in thyroid cancer mortality, JAMA Oncol. 3 (2) (2017) 202–208, https://doi.org/10.1001/JAMAONCOL.2016.3288.

[27] A. Coca-Pelaz, J.P. Shah, J.C. Hernandez-Prera, et al., Papillary thyroid cancer—aggressive variants and impact on Management: a narrative review, Adv. Ther. 37 (7) (2020) 3112, https://doi.org/10.1007/S12325-020-01391-1.

[28] J. Tang, D. Kong, Q. Cui, et al., Racial disparities of differentiated thyroid carcinoma: clinical behavior, treatments, and long-term outcomes, World J. Surg. Oncol. 16 (1) (2018) 1–9, https://doi.org/10.1186/S12957-018-1340-7/TABLES/4.

[29] H. Zheng, V. Lai, J. Lu, et al., Comparing the rate and extent of malignancy in surgically excised thyroid nodules across race and ethnicity, Am. J. Surg. 223 (4) (2022) 617–623, https://doi.org/10.1016/J.AMJSURG.2021.09.018.

[30] A. Finlayson, I. Barnes, S. Sayeed, B. McIver, V. Beral, R. Ali, Incidence of thyroid cancer in England by ethnic group, 2001–2007, Br. J. Cancer 110 (5) (2014) 1322–1327, https://doi.org/10.1038/bjc.2014.4, 2014 110:5.

[31] L. Fejerman, N. Ahmadiyeh, D. Hu, et al., Genome-wide association study of breast cancer in Latinas identifies novel protective variants on 6q25, Nat. Commun. 5 (2014) 5260, https://doi.org/10.1038/NCOMMS6260, 5260.

[32] J. Hoffman, L. Fejerman, D. Hu, et al., Identification of novel common breast cancer risk variants at the 6q25 locus among Latinas, Breast Cancer Res. 21 (1) (2019), https://doi.org/10.1186/S13058-018-1085-9.

[33] C. La Vecchia, M. Malvezzi, C. Bosetti, et al., Thyroid cancer mortality and incidence: a global overview, Int. J. Cancer 136 (9) (2015) 2187–2195, https://doi.org/10.1002/IJC.29251.

[34] M.S. Sierra, I. Soerjomataram, D. Forman, Thyroid cancer burden in central and South America, Cancer Epidemiol 44 (Suppl 1) (2016) S150–S157, https://doi.org/10.1016/J.CANEP.2016.07.017.
[35] M. Carlberg, L. Hedendahl, M. Ahonen, T. Koppel, L. Hardell, Increasing incidence of thyroid cancer in the Nordic countries with main focus on Swedish data, BMC Cancer 16 (1) (2016) 1–15, https://doi.org/10.1186/S12885-016-2429-4/FIGURES/11.
[36] V. Espinosa, D. De La Torre, C. Acuña, C. Cadena, [Human resources for health in Ecuador's new model of care], Rev Panam Salud Publica 41 (2017), https://doi.org/10.26633/RPSP.2017.52.
[37] E. Ortiz-Prado, J. Ponce, F. Cornejo-Leon, et al., Analysis of health and drug access associated with the purchasing power of the Ecuadorian population, Glob J Health Sci 9 (1) (2016) p201, https://doi.org/10.5539/GJHS.V9N1P201.
[38] D. Garzon-Chavezi, D. Romero-Alvarez, M. Bonifaz, et al., Adapting for the COVID-19 pandemic in Ecuador, a characterization of hospital strategies and patients, PLoS One 16 (5) (2021), https://doi.org/10.1371/JOURNAL.PONE.0251295.
[39] I.C. Nettore, A. Colao, P.E. Macchia, Nutritional and environmental factors in thyroid carcinogenesis, Int J Environ Res Public Health 15 (8) (2018), https://doi.org/10.3390/IJERPH15081735.
[40] N. Montero-Oleas, S. Núñez-González, D. Simancas-Racines, The remarkable geographical pattern of gastric cancer mortality in Ecuador, Cancer Epidemiol 51 (2017) 92–97, https://doi.org/10.1016/J.CANEP.2017.10.014.
[41] R. Vigneri, P. Malandrino, F. Gianì, M. Russo, P. Vigneri, Heavy metals in the volcanic environment and thyroid cancer, Mol. Cell. Endocrinol. 457 (2017) 73–80, https://doi.org/10.1016/J.MCE.2016.10.027.
[42] E.L. Gavilanez, K. Guerrero Franco, A. Segale Bajaña, et al., Trends of thyroid cancer mortality rates in Ecuador, J Endocrinol Diabetes 5 (5) (2018) 1–6, https://doi.org/10.15226/2374-6890/5/5/001114.
[43] P. Solis-Pazmino, J. Cucalon, G. Jaramillo-Koupermann, et al., High Prevalence of BRAF V600E Mutation in Patients with Papillary Thyroid Cancer from Northern Ecuadorian Andes, 2018.
[44] F.A. Rashid, J. Munkhdelger, J. Fukuoka, A. Bychkov, Prevalence of BRAFV600E mutation in Asian series of papillary thyroid carcinoma—a contemporary systematic review, Gland Surg. 9 (5) (2020) 1878, https://doi.org/10.21037/GS-20-430.
[45] A.P. Estrada-Flórez, M.E. Bohórquez, A. Vélez, et al., BRAF and TERT mutations in papillary thyroid cancer patients of Latino ancestry, Endocr Connect 8 (9) (2019) 1310, https://doi.org/10.1530/EC-19-0376.
[46] C. Alina Silaghi, C. Emanuela Georgescu, Silaghi tiu, R. Aurelian Tiucă, O. Mirela Tiucă, I. Maria Pas, The role of genetic polymorphisms in differentiated thyroid cancer: a 2023 update, Biomedicines 11 (2023) 1075, https://doi.org/10.3390/BIOMEDICINES11041075, 2023;11(4):1075.
[47] J. Hlozek, B. Pekova, J. Rotnagl, R. Holy, J. Astl, Genetic changes in thyroid cancers and the importance of their preoperative detection in relation to the general treatment and determination of the extent of surgical intervention—a review, Biomedicines 10 (7) (2022), https://doi.org/10.3390/BIOMEDICINES10071515.
[48] A. Guerra, P. Zeppa, M. Bifulco, M. Vitale, Concomitant BRAF(V600E) mutation and RET/PTC rearrangement is a frequent occurrence in papillary thyroid carcinoma, Thyroid 24 (2) (2014) 254–259, https://doi.org/10.1089/THY.2013.0235.
[49] M. Zou, E.Y. Baitei, A.S. Alzahrani, et al., Concomitant RAS, RET/PTC, or BRAF mutations in advanced stage of papillary thyroid carcinoma, Thyroid 24 (8) (2014) 1256–1266, https://doi.org/10.1089/THY.2013.0610.
[50] S. Franceschi, F. Lessi, F. Panebianco, et al., Loss of c-KIT expression in thyroid cancer cells, PLoS One 12 (3) (2017), e0173913, https://doi.org/10.1371/JOURNAL.PONE.0173913.
[51] S. Tomei, C. Mazzanti, I. Marchetti, et al., c-KIT receptor expression is strictly associated with the biological behaviour of thyroid nodules, J. Transl. Med. 10 (1) (2012) 1–9, https://doi.org/10.1186/1479-5876-10-7/TABLES/6.
[52] A. Acuña-Ruiz, C. Carrasco-López, P. Santisteban, Genomic and epigenomic profile of thyroid cancer, Best Pract Res Clin Endocrinol Metab 37 (1) (2023), 101656, https://doi.org/10.1016/J.BEEM.2022.101656.