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BRAF mutation distribution according to epidemiological and histopathological characteristics in papillary thyroid cancer. A single-center observational study

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Abstract

Introduction: Thyroid cancer is positioned as one of the most prevalent neoplasms in Ecuador, typically manifesting in the fourth decade of life, with a higher incidence in women. The predominant histological subtype is papillary carcinoma (PTC), and various studies present shown that up to 80% of PTC cases present the BRAF mutation. This mutation has been associated with unfavorable prognostic factors, such as the presence of lymph node metastases, advanced tumor stages, extrathyroidal extension, and aggressive histological features. Additionally, a correlation has been observed with a higher recurrence rate and a reduced response to iodine treatment. Given this context, this research aims to analyze the distribution of the BRAF mutation according to epidemiological and histopathological characteristics in patients diagnosed with papillary thyroid cancer in Ecuador.

Materials and methods: This retrospective descriptive study involved the analysis of genetic data from 106 medical records of patients diagnosed with papillary thyroid cancer who underwent BRAF mutation detection. The sample was selected based on established criteria.

Results: Evaluation of medical records revealed the presence of the BRAF mutation in 75% of cases. This percentage was higher in women, individuals over 45 years of age, and residents in urban areas. Regarding occupation, most patients were dedicated to cleaning work and had no personal history of exposure to ionizing radiation or a family history of cancer. Additionally, 84% of the patients were in clinical stage I and the neoplasms were located in the right thyroid lobe.

Conclusion: This analysis highlights the urgent need to identify risk factors linked to the appearance of papillary thyroid carcinoma in the Ecuadorian population. The results indicate a significant prevalence of the BRAF mutation, underlining its relevance as a prognostic marker in this disease. These findings may contribute to a better understanding of the epidemiology and pathogenesis of thyroid cancer leading to improvements in prevention and treatment strategies at the local level.

Keywords:
DeCS: Thyroid cancer; Thyroid Cancer, Papillary; Proto Oncogene, Proteins BRAF.

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Introduction

Thyroid cancer is considered the most common endocrine neoplasia, accounting for 3% of all malignant tumors [1, 2]. Among Latin American countries, Ecuador has the highest incidence of this type of neoplasia [3]. It occurs more frequently in women, who are three times more likely to be affected than men [4, 5]; the mean age of presentation is around the fourth decade of life [6–8]. Among the risk factors, exposure to ionizing radiation and certain substances found in cleaning and disinfection products, pesticides, solvents, and industrial factory products are evident [9, 10].

Various histological types of thyroid cancer have been recognized, with the papillary carcinoma (PTC) variant being the most common among the different histological types [11]. Different genetic alterations are associated with thyroid carcinoma, and the most relevant alteration in PTC is the BRAF mutation.

This mutation is related to various cellular processes, such as cell growth, division, and differentiation, all closely related to cancer pathogenesis. In PTC, up to 80% of the mutations in this gene are detected, with alterations that specifically occur at the level of V600F, where valine is replaced by glutamine at codon 600 [12, 13].

Several authors agree that there is a relationship between the age of presentation of PTC and the frequency of the BRAF mutation. This relationship is more significant in patients older than 45 years. Furthermore, this cutoff point may synergistically affect the mutation, worsening the prognosis [14, 15]. This finding is supported by other studies demonstrating that the mortality risk is greater in patients older than 45 years of age only when BRAF is positive. Therefore, age, as an independent variable, is not associated with patient mortality. [16, 17]. Similarly, a synergistic interaction between the BRAF mutation and age ≥60 years has been demonstrated concerning recurrence, even in low-risk patients corresponding to stages I and II of the disease. [18]. Although there are currently diverse criteria and results regarding the relationship of the BRAF V600E mutation with thyroid cancer, several studies agree that the presence of the mutation is associated with aggressive characteristics, such as the presence of lymph node metastases [4, 12, 15], advanced tumor stage (precise stage III and IV), [12, 15, 19], extrathyroidal extension [19] and aggressive histological features [4, 12].

Finally, studies on response to treatment show that the BRAF mutation is associated with a low expression of sodium iodide symporter genes, making these tumors refractory to radioactive iodine therapy. Furthermore, it is closely related to the elevation of serum thyroglobulin after treatment with iodine 131, which reflects its low effectiveness, so detecting the mutation before treatment can predict treatment results [12, 14].

The general objective of the research is to determine the distribution of BRAF according to epidemiological and histopathological characteristics in patients diagnosed with papillary thyroid cancer treated at SOLCA-CUENCA from 2019 to 2020. The specific objectives of this study were to characterize the study population demographically, establish the frequency of BRAF mutations in patients with papillary thyroid cancer, and determine the distribution of BRAF mutations in relation to the described variables. We find it essential to conduct this study due to the high incidence and prevalence of thyroid cancer in our environment and the limited local information available. Describing, studying, and investigating genetic mutations enable us to predict the disease's progression and define molecular classifications for distinct treatment groups.

Materials and methods

Design of the investigation
Descriptive, retrospective, cross-sectional study

Scenery
The study was carried out at the National Oncology Institute SOLCA - Cuenca. The study period was from 2019 to 2020.

Universe and sample
Our study involved the total population of patients diagnosed with PTC at the SOLCA Cancer Institute (Cuenca) between 2019 and 2020. No sampling was employed, because of what was previously mentioned.

Participants
The complete medical records of patients, whether men or women, of all ages who were diagnosed with papillary thyroid cancer, with or without the BRAF mutation, at the Cuenca SOLCA Cancer Institute from 2019 to 2020, were included. Patients who did not have papillary thyroid cancer, those with papillary thyroid cancer who had not undergone BRAF mutation testing, and those with incomplete medical records were excluded.

Variables

The variables encompassed sex, age, individual history of ionizing radiation exposure, family history of cancer, occupation, residence, site of injury, clinical stage, and the outcome of the BRAF mutation.

Research procedure
The method used was indirect observation. The information related to the study variables were extracted from each of the medical records through the computer system of SOLCA-Cuenca. A form designed to record data were developed to include the abovementioned variables.

Statistic analysis

Clinical data and statistical analyses were conducted using SPSS 22.0 free version software. Frequency tables showing absolute and relative counts were created for qualitative variables, while measures of central tendency and dispersion were calculated for quantitative variables. The odds ratio was used to quantify the risk of recurrence associated with the BRAF mutation.

Results

Participants
A total of 106 cases that met the inclusion criteria were analyzed. The average age is 46.4 ± 14.7 years. 88% of cases were women (Table 1)

Table 1. Distribution of 106 patients with papillary thyroid cancer according to age, sex, and residence, SOLCA – Cuenca 2019-2020.

Epidemiological Factors	Frequency (N=106)	Percentage 100%
Age		
10-19 years	2	2
20-29 years	9	8
30-39 years	29	27
40-49 years	21	20
50-59 years	26	25
60-69 years	10	9
70-79 years	9	8
Sex		
Man	18	17
Women	88	83
Home		
Rural	16	15
Urban	90	85

The majority of patients were dedicated to cleaning (48%). There was individual history of ionizing radiation exposure (Table 2).

Table 2. Distribution of 106 patients with papillary thyroid cancer according to occupation and individual history of ionizing radiation exposure, SOLCA – Cuenca.

Epidemiological Factors	Frequency (N=106)	Percentage 100%
Occupation		
Agriculture	3	3
Construction and mining	2	2
Cleaning	51	48
Professional	22	21
Security	1	1
Transport	1	1
Sales	17	16
Unemployed	9	8
Personal history of exposure to ionizing radiation		
Yeah	0	0
No	100	100
Family cancer history		
Yeah	30	28
No	76	72

Main results

80% of cases had a positive histopathological marker. Most cases were in clinical stages I and II the right lesion site (Table 3). There were no associations found with the study variables, except for clinical stage II, identified as a protective factor (Table 4). (Table 4).

Table 3. Distribution of 106 patients with papillary thyroid cancer according to BRAF mutation, clinical stage, and lesion site, SOLCA - Cuenca 2019-2020.

Histopathological Factors	Frequency (N=106)	Percentage 100%
BRAF Positive	80	75
BRAF Negative	26	25
Clinical stage		
Yo	85	80
II	15	14
III	2	2
IV	4	4
Injury site		
Right	61	58
Left	40	38
Isthmus	5	5

Table 4. Distribution of the mutation of 106 patients according to age, sex, individual history of ionizing radiation exposure, family oncological history, clinical stage, and site of injury, SOLCA – Cuenca 2019-2020.

	BRAF Positive N=80	BRAF Negative N=26	OR	CI 95%	*P*
Age					
<45 years	36 (45%)	15 (58%)	0.66	0.2454-1.4670	0.2628
>45 years	44 (55%)	11 (42%)			
Sex					
Women	68 (85%)	20 (77%)	1,700	0.5661-5.1047	0.3442
Man	12 (15%)	6 (23%)			
Home					
Urban	67 (84%)	23 (88%)	0.6722	0.1757-2.5719	0.5618
Rural	13 (16%)	3 (12%)			
Occupation					
Agriculture	3. 4%)	0 (0%)	2.3935	0.1197-47.878	0.5680
Construction and mining	2 (2%)	0 (0%)	1.6879	0.0785-36.295	0.7381
Cleaning	39 (48%)	12 (50%)	1.1098	0.4571-2.6943	0.8180
Professional	19 (23%)	3 (13%)	2.3880	0.6452-8.8389	0.1924
Security	eleven%)	0 (0%)	1.0000	0.0395-25.298	1,000
Transport	eleven%)	0 (0%)	1.0000	0.0395-25.298	1,000
Sales	12 (15%)	5 (21%)	0.7412	0.2341-2.3463	0.6104
Unemployed	5 (6%)	4 (17%)	0.3667	0.0906-1.4850	0.1596
Radiation exposure					
Yes	0 (0%)	0 (0%)	-	-	-
No	80 (100%)	26 (100%)			
Relatives with a history of oncology					
Yes	24 (30%)	6 (23%)	1.4286	0.5100-4.0017	0.4973
No	56 (70%)	20 (77%)			
Clinical stage					

Yes	67 (84%)	18 (60%)	2.2906	0.8235-6.3712	0.1123
II	7 (9%)	8 (27%)	0.2158	0.0691-0.6733	0.0083
III	23%)	0 (0%)	1.6879	0.0785-36.294	0.7381
IV	Four. Five%)	0 (0%)	3.1176	0.1624-59.865	0.4507
Site of injury					
Right	47 (59%)	14 (54%)	1.2208	0.5012-2.9737	0.6605
Left	30 (38%)	10 (38%)	0.9600	0.3862-2.3863	0.9300
Isthmus	3. 4%)	2 (8%)	0.4675	0.0737-2.9644	0.4198

Discussion

In the present investigation, the average age at the presentation of papillary thyroid cancer was 46.4 years; the majority of our patients were women (83%) and residents of urban areas (85%), thus confirming that our results are aligned with those observed in other studies. In the study conducted by Velázquez et al., the mean age at presentation was 43 years, with 85.7% being women [20]; Huang et al. reported a mean age of 43.3 years, with 75.7% being women [7] Zeng et al. obtained a mean age of 42.3 years, with 84.1% being women [8]. In research carried out in our country, Sánchez et al. determined that the mean age of presentation ranged between 40 and 49 years, with 83% of the patients being women [21]. Salazar et al. had an average age of 49 years, where 80% were women; the latter also identified that 90% of the cases belonged to urban areas [3].

By demonstrating that this type of cancer occurs mainly during the fourth and fifth decades of life, associated risk factors such as personal and family history and lifestyle must be considered. Studies have shown that estrogen significantly increases the proliferation of thyroid cancer cells [20, 23]. Furthermore, a relationship between pharmaceutical estrogens and the development of thyroid cancer has been found [24]; this could explain why their frequency was greater in women. Patients who reside in urban areas in our country generally have greater access to health services and early diagnosis of pathologies, which may be linked to the results of our research.

Several authors have established a critical association between exposure to ionizing radiation and the occurrence of thyroid cancer [25]. However, according to the results of the present investigation, no patient presented this history. This absence may be related to the presence of other risk factors or a lack of awareness about potential exposure to ionizing radiation, possibly during childhood.

In a study published by Ba et al., the results demonstrated a higher risk of developing papillary thyroid carcinoma among health personnel, including professionals involved in disease diagnosis and treatment. Moreover, they identified an increased risk in cleaning and pest control workers [10]. In the present study, individuals whose occupation involved cleaning-related activities were predominant (48%). This leads us to infer a connection between exposure to different substances in cleaning products in our environment and the occurrence of neoplasms.

Regarding family oncological history, 28% of the patients studied had a history of it. Likewise, in a study conducted by Khan et al., 2% had a family history of cancer [26]. Considering that only a few studies have demonstrated this correlation, further research in this field is needed.

Molecular studies have significantly impacted diseases, especially in malignant proliferations, since they allow groups to be established from a genetic point of view. In the present study, BRAF mutation existed in 75% of the cases; Several investigations have demonstrated similar results. For, Pessoa-Pereira et al. published work with 43 patients showing BRAF positivity in 65.1% [27], and Vieira et al., with 45 patients, showed BRAF positivity in 66.7% [28].

In our research, we examined the distribution of cases with BRAF mutations compared to other variables. We observed a higher proportion in patients over the age of 45, women, residents of urban areas, and those with occupations involving cleaning activities. Additionally, we found cases with no history of radiation exposure, predominantly without references to family cancer history, diagnosed at clinical stage I, with the right lobe being the most affected. Some of these findings align with several publications.

Yan et al. analyzed 2048 patients with papillary thyroid cancer, of whom 1715 had a BRAF mutation, and did not find any differences in terms of sex, determined that patients were more likely to carry the mutation as they aged; Furthermore, it demonstrated a higher incidence of said mutation in patients with a family oncological history. The location of the lesion in patients presenting the genetic mutation was mainly bilateral multifocal and in clinical stages III and IV [15], similar to the study by Lu et al. Out of the 108 patients with papillary thyroid cancer, 59 had a mutation in the BRAF gene; this mutation occurred in 65.1% of individuals older than 45 years, 53.1% were women, and the site of injury corresponded to the right thyroid lobe with 55.9% [29].

It should be noted that, according to our research, the absence of the BRAF mutation was primarily found in patients under 45 years of age, unlike those who did present the mutation. Furthermore, although the patients who showed the BRAF mutation were mainly in clinical stage I, 3% were in clinical stage III, and 5% were in clinical stage IV. In contrast, those who did not present the mutation were only found in clinical stages I and II. Ge et al. determined that the BRAF mutation was related to age ≥45 years; conversely, it did not demonstrate a significant correlation with metastasis or clinical stage [14]. Shen et al. found a higher percentage of patients in clinical stage III and IV in patients with BRAF mutation [16]. Dominguez et al. found that 80% of patients in stages III and IV had the BRAF mutation, while 57.1% of patients with stages I and II did not have the mutation; they found no differences in sex or lesion location [12].

Several authors agree that the presence of this mutation constitutes a prognostic factor and influences the response to treatment of the disease [2, 14]; the study conducted by Lu et al. establishes that it is of great importance to develop the relationship between the molecular mechanisms with their clinicopathological characteristics, giving relation to the aggressive behavior of the tumor [19]; Furthermore, Paja et al. mentions that the gene mutation is related to a worse prognosis and a more remarkable recurrence of the disease, which is why its study is essential [30].

Conclusions

The distribution of papillary thyroid carcinoma in our population according to sex and age is similar to studies in other regions. It is striking that none of the studied patients reported a

history of exposure to ionizing radiation, a significant risk factor for developing this neoplasia. For this reason, we consider the importance of further investigating other risk factors in our population. It was identified that the occupation of most patients was cleaning work. Therefore, it is necessary to promote studies that identify the chemical composition of cleaning products in our environment, their relationship with oncogenesis, and the protective measures used by personnel.

It was found that the majority of patients had the BRAF mutation. These results agree with the documented literature, which indicates that this mutation is one of the most frequent in papillary thyroid carcinoma. We found that most of the mutation occurred in people over 45. Furthermore, although papillary carcinoma is a slow-growing neoplasm, cases in advanced clinical stages were found only in patients carrying the BRAF mutation.

As thyroid cancer is one of the most frequent neoplasms with high incidence rates, we recognize that it is imperative to carry out more research in the area in our environment and recognize factors associated with its appearance with the aim of promoting prevention activities, early detection, adequate staging, and timely treatment.

Abbreviations

BRAF : B-RAF proto-oncogene.

Administrative information

Additional Files

None declared by the authors.

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Author contributions

Ximena Estefanía Mendieta Álvarez: Conceptualization, data curation, formal analysis, acquisition of funds, research, writing - original draft.

Doménica Carolina Patiño Murillo: Conceptualization, Data curation, Formal analysis, Marx Ítalo Bravo Muñoz: Fund acquisition, Research, Methodology, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review and editing.

All authors read and approved the final version of the manuscript.

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Availability of data and materials

Data are available upon request to the corresponding author. No other materials are reported.

Statements

Ethics committee approval
COBIAS, the Health Research Bioethics Committee of the University of Cuenca, approved the study.

Informed consent
Not required when patient-specific images, MRIs, or CT studies are not published.

Conflicts of interest
The authors declare no conflict of interest.

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