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THE ROLE OF BRAF V600E IN THE DEVELOPMENT OF THYROID CANCER PHENOTYPE: A SYSTEMATIC REVIEW

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ABSTRAK

Mutasi BRAF V600E pada kanker tiroid belakangan menjadi perhatian utama karena hubungannya dengan peningkatan agresivitas tumor melalui aktivasi jalur MAPK yang memengaruhi karakteristik fenotipik seperti morfologi dan pola invasi. Hasil penelitian efek mutasi ini sering bervariasi dan dipengaruhi perbedaan dalam desain studi dan metode deteksi. Tinjauan sistematis ini bertujuan mengklarifikasi hubungan antara BRAF V600E dan karakteristik fenotipik PTC. Metode penelitian ini adalah *systematic literature review* dengan metode PRISMA dan didapat 8418 jurnal. Setelah eksklusi, ditemukan artikel yang sesuai sebanyak 16 jurnal artikel. Berdasarkan hasil telaah ditemukan hubungan mutasi BRAF V600E terhadap fenotipe kanker tiroid seperti gender perempuan, usia lebih tua saat diagnosis, ukuran tumor lebih besar, subtipe histologi *tall cell*, skor nukleus lebih tinggi, invasi kapsul, ekstratiroid, vaskuler, saraf, metastasis limfonodus, stadium klinis lebih tinggi, kekambuhan dan survival lebih rendah. Meskipun demikian, terdapat penelitian yang inkonsisten mengenai hubungan mutasi ini dengan karakteristik fenotipe tersebut. Mutasi BRAF V600E secara signifikan mempengaruhi karakteristik fenotipik kanker tiroid dan dikaitkan dengan karakteristik agresif.

ABSTRACT

The Role of BRAF V600E in The Development of Thyroid Cancer Phenotype: a Systematic Review. BRAF V600E mutation in thyroid cancer is of major concern because it is associated with increased tumor aggressiveness through the MAPK pathway activation that affects phenotypic characteristics such as morphology and tissue invasion patterns. The results of studies on the effects of this mutation often vary and are influenced by differences in study design and detection methods. This systematic review aims to clarify the relationship between BRAF V600E and phenotypic characteristics of PTC, as well as identify its clinical implications. This study method was a systematic literature review using the PRISMA method, and there were 8418 journals. After exclusion, 16 articles were found that met the research objectives. Based on the results, it was found that there was a relationship between BRAF V600E and thyroid cancer phenotypes such as female gender, older age at diagnosis, larger tumor size, histological subtypes, especially tall cell, higher nuclear score, capsule, extrathyroidal, vascular, nerve invasion, lymph node metastasis, higher clinical stage, recurrence, and lower survival. However, there are other inconsistent studies regarding the association of BRAF V600E with these phenotype characteristics. BRAF V600E mutation significantly affects the phenotypic characteristics of thyroid cancer and is associated with several aggressive characteristics.

INTRODUCTION

Thyroid cancer, especially papillary thyroid carcinoma (PTC), is one of the most common types of endocrine cancer with an increasing incidence in recent decades.[1] Among the various genetic factors involved, the BRAF V600E mutation has been a major focus of research because of its association with increased tumor aggressiveness and poor clinical outcomes.[2,3]

BRAF V600E is a somatic mutation that activates the mitogen-activated protein kinase (MAPK) pathway, which regulates cell proliferation and differentiation.[4] Previous studies have shown that BRAF V600E affects tumor behavior and histological and phenotypic characteristics, such as cell morphology and tissue invasion patterns.[5,6] However, although several studies show an association between this mutation and clinical characteristics, the results are often variable, and there is no clear consensus on how BRAF V600E specifically affects phenotypic aspects.[7]

This gap in understanding is partly due to variations in study design, populations studied, and methods used to detect mutations and assess phenotypic characteristics. Therefore, it is important to conduct a systematic review that collects and analyzes existing data to gain deeper insight into the impact of the BRAF V600E mutation on the phenotypic characteristics of thyroid cancer.

This systematic review is expected to clarify the relationship between BRAF V600E and phenotypic characteristics of thyroid cancer, as well as identify the clinical implications of these findings. The results of this study are expected to significantly contribute to a better understanding of the diagnosis and treatment of thyroid cancer and pave the way for further research in this field.

METHODS

This study uses a systematic review method to identify, evaluate, and interpret all primary research results related to the research question, a particular topic, or a phenomenon of interest, aiming to combine and understand the research and present more comprehensive facts. The systematic review method is applied in this study by referring to the PRISMA (Preferred Reporting Items for Systematic Reviews & Meta-Analyses) guidelines, which help compile and report research findings systematically.

Search strategy

The data search strategy starts with searching for data and/or information sources, selecting studies through quality assessment according to eligibility criteria and quality assessment instruments, and extracting data. The keywords used in the literature search were "BRAF V600E" OR "BRAF mutation" OR "BRAF gene" OR "BRAF V600E mutation" AND "thyroid cancer" OR "thyroid carcinoma" OR "thyroid neoplasm" AND "phenotypic characteristics" OR "phenotype" OR "morphology" OR "pathology" OR "characteristics" OR "features."

Information Sources

A literature search was conducted using online databases. The online databases used in the literature search were PubMed and Google Scholar.

Eligibility Criteria

The eligibility criteria in this study consist of inclusion and exclusion criteria. The inclusion criteria set are articles in the form of research articles and not literature reviews, article sources come from PubMed and Google Scholar, the full text can be accessed and open access in English with the year of publication of the article is the last 5 years, namely 2019-2024. The exclusion criteria in this study are articles that need PICO (Population, Intervention, Comparison, Outcome) consistent with the research objectives and duplicate articles. PICO details are presented in Table 1.

Table 1. PICO Summary

Component	Information
Population	Thyroid cancer patients with BRAF V600E mutation
Intervention	The presence or absence of the BRAF V600E mutation
Comparison	Thyroid cancer patients without BRAF V600E mutation
Outcome	Phenotypic characteristics (e.g., cell differentiation, tissue invasion, etc.)

Quality Assessment

The literature was searched using the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) method through four stages: identification, screening, eligibility, and included results. The Prisma Flow Diagram in this study can be seen in Figure 1.

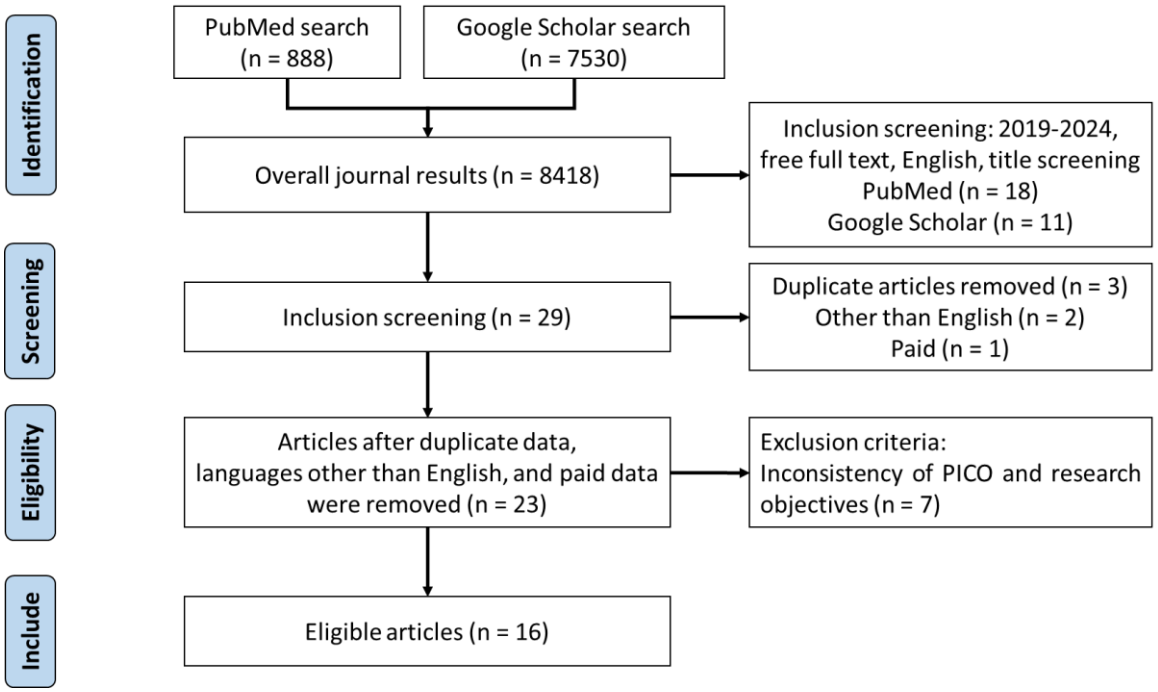

Figure 1. PRISMA flow diagram.

Based on the literature search results with a systematic review, 8418 journals and articles were obtained with the keywords BRAF V600E thyroid cancer/carcinoma phenotype/pathological characteristics/features. A total of 8389 articles were excluded because they needed to meet the inclusion criteria for publication years 2019-2024 at the screening stage, full text, open access, and in English. A total of 3 articles were duplicated through screening based on the inclusion criteria. A total of 3 articles were excluded because they did not comply with PICO and the research objectives set. A total of 20 journal articles were obtained that were eligible according to PICO and the research objectives for this literature study.

Data Extraction

The output of data extraction is presented in the form of a table consisting of the study's title, the researcher's name, the year of publication, the research design, the population, the number of samples, the detection method, and the results.

RESULTS

After searching the two databases, 8418 articles related to the keywords adopted by the researcher were identified. Of these, three articles were duplicates, while seven had titles and abstracts that needed to be more relevant to the focus of the study. After applying the inclusion criteria, 16 articles were selected that met the requirements for further analysis (Table 2).

Table 2 Journal Description of the Relationship between BRAF V600E Mutation and PTC Phenotype Characteristics.

No.	Author, year, study design, title	Population, sample size	Methods	Results and conclusion
1	Hong X, et al (2024). Retrospective study. Retrospective study of BRAF V600E mutation and CT features of papillary thyroid carcinoma[8]	381 PTC patients	PCR from FNAC cytology sample dan CT scan analysis spectral Iqon	BRAF V600E mutation tends to be found in females with irregular tumor shapes.
2	Abdulhaleem M et al (2023). Cohort retrospective study. The Impact of BRAF V600E Mutation Allele Frequency on the Histopathological Characteristics of Thyroid Cancer[9]	44 thyroid malignancy patients with BRAF V600E positive	Next generation sequencing (NGS)	● BRAF V600E allele frequency (BRAF V600E AF) mutation is associated with aggressive PTC and lymph node involvement. ● BRAF V600E AF mutation is not significantly associated with PTC histologic subtype and nodule size.
3	Harahap AS et al (2023). Retrospective study. Developing Models to Predict BRAFV600E and RAS Mutational Status in Papillary Thyroid Carcinoma Using Clinicopathological Features and pERK1/2 Immunohistochemistry Expression[3]	222 PTC patients	Sanger sequencing (BRAF) dan IHK (pERK1/2)	● BRAF V600E mutation is significantly associated with aggressive characteristics of PTC patients. ● Several independent predictors of BRAF mutation are nuclear score 3, absence of capsule, aggressive histological subtype, and pERK 1/2 level more than 10%.

4	Harahap AS et al (2023). Retrospective study. Profile of BRAFV600E, BRAFK601E, NRAS, HRAS, and KRAS Mutational Status, and Clinicopathological Characteristics of Papillary Thyroid Carcinoma in Indonesian National Referral Hospital[10]	172 PTC patients after total thyroidectomy	PCR and sequencing DNA	BRAF V600E mutation is significantly associated with high clinical stage, tall cell variant, non-capsular morphology, lymphovascular invasion, extrathyroid extension, and lymph node metastasis in PTC.
5	Ozcelic S et al (2019). Retrospective study. BRAF V600E mutation in papillary thyroid cancer is correlated with adverse clinicopathological features but not with iodine exposure[11]	PTC patients	Sequencing DNA	● Significant correlation between BRAF V600E mutation and characteristics such as age, advanced tumor stage (T4), vascular and thyroid capsule invasion, extrathyroid tissue invasion, and lymph node metastasis. ● BRAF V600E mutation is associated with more aggressive disease characteristics in PTC.
6	Perczak DG et al (2019). Cohort Retrospective study. Coexisting Germline CHEK2 and Somatic BRAFV600E Mutations in Papillary Thyroid Cancer and Their Association with Clinicopathological Features and Disease Course[12]	427 PTC patients	PCR	● BRAF V600E mutation is associated with older patient age and extrathyroidal extension. ● Conclusion: The coexistence of BRAF V600E and CHEK2 mutations is not associated with a more aggressive disease course or worse outcome.
7	Pereira DP et al (2019). Retrospective study. Association between BRAF (V600E) mutation and clinicopathological features of papillary thyroid carcinoma: a Brazilian single-center case series[13]	43 PTC patients	PCR	● The proportion of the BRAF mutation group was significantly higher in older age. PTC patients with Hashimoto's thyroiditis were less likely to have BRAF mutation. ● Conclusion: Older age and absence of Hashimoto's thyroiditis were independently associated with the presence of BRAF (V600E) mutation in PTC patients.
8	Shi C et al. (2020). Retrospective study. BRAFV600E mutation, BRAF-activated long non-coding RNA and miR-9 expression in papillary thyroid carcinoma, and their association with clinicopathological features[14]	51 PTC patients	PCR	● BRAF V600E mutation is associated with larger tumor size, higher bilaterality, multifocality, extracapsular invasion, and lateral lymph node metastasis. ● Conclusion BRAF V600E mutation is associated with more aggressive PTC features. ● This molecular marker may indicate the need for more aggressive initial surgical management, including

				total thyroidectomy, to reduce recurrence.
9	Xie M et al (2024). Retrospective study. Correlation Between the Clinicopathological Features of Papillary Thyroid Carcinoma Complicated with Hashimoto's Thyroiditis, BRAF V600E Gene Mutation, and RET Gene Rearrangement[15]	150 PTC patients	IHK VE1	● The prevalence of PTC concurrent with Hashimoto's thyroiditis was higher in women, the incidence of lymph node metastasis was lower, and the proportion of small tumors (<1 cm) was higher. ● The positivity rate of BRAF V600E was lower in patients with PTC concurrent with Hashimoto's thyroiditis. ● Hashimoto's thyroiditis may alter the molecular profile of PTC and influence the choice of therapy.
10	Zhang M et al (2022). Retrospective study. Combined expression of the BRAFV600E mutation and PD-L1 in early papillary thyroid carcinoma and its relationship with clinicopathological features and recurrence—a retrospective cohort study[16]	137 early-stage PTC patients	IHK VE1	● In early-stage PTC, BRAF V600E mutation is associated with Hashimoto's thyroiditis. ● BRAF V600E mutation is not associated with gender, age at diagnosis, tumor size, multifocality, capsular invasion, extra glandular invasion, lymphatic, vascular, and nerve invasion, and CLNM. ● The combination of BRAF V600E mutation and PD-L1 expression is not a predictor of recurrence in early-stage PTC.
11	Wang Z et al (2022). Retrospective study. Genetic and Clinicopathologic Characteristics of Papillary Thyroid Carcinoma in the Chinese Population: High BRAF Mutation Allele Frequency, Multiple Driver Gene Mutations, and RET Fusion May Indicate More Advanced TN Stage[17]	395 PTC patients	Second generation sequencing	● BRAF mutant allele frequency (MAF) was associated with a higher risk of lymph node metastasis, lateral lymph node metastasis, and higher tumor stage (T3/T4). ● Conclusion: High BRAF MAF (>16.93%) was associated with increased aggressiveness and lymph node metastasis in PTC patients in China.
12	Tabriz N et al (2020). Retrospective study. BRAF V600E mutation correlates with aggressive clinicopathological features but does not influence tumor recurrence in papillary thyroid carcinoma—10-year single-center results[18]	186 PTC patients	PCR	● BRAF V600E mutation was found to be significant in older patients with smaller tumor size, multifocality, and extracapsular invasion (stage T3b and T4a). ● BRAF-positive tumors had higher levels of infiltration in the lateral lymph node compartment and distant metastasis. ● No difference in recurrence with BRAF-negative tumors.

				● BRAF-positive PTCs are associated with more aggressive tumor characteristics but do not necessarily have a higher recurrence rate at 5-year follow-up.
13	Li G et al (2020). Retrospective study. Predictive Factors for Level V Lymph Node Metastases in Papillary Thyroid Carcinoma with BRAFV600E Mutation and Clinicopathological Features[19]	252 PTC patient after neck lymph node dissection	Sequencing DNA	BRAF V600E mutation was significantly associated with several aggressive traits such as patient age, presence of lymphocytic thyroiditis, capsular invasion, bilateral central lymph node metastasis, and level V lymph node metastasis.
14	Gao J et al (2019). Retrospective study. Associations of the BRAF V600E Mutation and PAQR3 Protein Expression with Papillary Thyroid Carcinoma Clinicopathological Features[20]	60 post-surgical PTC patients	RT PCR	● BRAF V600E mutation was significantly associated with lymph node metastasis, but there was no significant association with other clinicopathological features such as tumor size, patient age, and multifocality. ● Conclusion: BRAF V600E mutation is associated with invasive PTC features, namely lymph node metastasis and extrathyroid extension.
15	Bandoh N et al (2023). Retrospective study. BRAF V600E mutation co-existing with oncogenic mutations is associated with aggressive clinicopathologic features and poor prognosis in papillary thyroid carcinoma[21]	130 PTC patients	NGS	● BRAF V600E mutation is associated with tracheal invasion and bilateral cervical lymph node metastasis. ● There is no significant difference in clinicopathological features between the no mutation group and the BRAF V600E mutation group.
16	Al Masri M et al (2021). Cohort Retrospective study. BRAF V600E mutation in papillary thyroid carcinoma: its relation to clinical features and oncologic outcomes in a single cancer center experience[22]	128 histologically confirmed PTC patients	Sequencing DNA	● BRAF V600E mutation is associated with smaller tumor size than no mutation. ● BRAF mutation is not associated with disease-free survival (DFS) or overall survival (OS). ● Conclusion: BRAF V600E mutation does not affect loco-regional recurrence, distant metastasis, or survival outcomes in PTC patients.

DISCUSSION

Table 2 shows that 16 articles were reviewed in this systematic review. These articles consist of retrospective studies, with 3 being retrospective cohort studies. The methods of detecting BRAF mutations in these studies used IHK VE1, PCR, DNA sequencing, and next-generation sequencing. These studies suggest that BRAF V600E mutations significantly affect the phenotypic characteristics of thyroid cancer, especially PTC.

BRAF mutations are said to be associated with histological subtypes, especially tall cell variants, according to research from Indonesia, namely research by Harahap et al.[3] The association of BRAF V600E mutation with histological subtype was not mentioned in the majority of other studies. In addition to the histological subtype, Harahap et al. associated BRAF V600E mutation with a higher nuclear score and distinctive biological behavior compared to RAS mutation.[3,10] Harahap et al. also proposed a predictive model of BRAF V600E mutation from certain variables that can help in clinical assessment.[3]

Abdulhaleem et al. found a higher frequency of BRAF V600E mutation alleles associated with aggressive histopathological features and positive sentinel lymph nodes. This can be a prognostic marker of tumor behavior in cases of thyroid malignancy. In contrast to Harahap et al., Abdulhaleem stated no significant association exists between BRAF V600E mutations and histological subtypes and nodule size.[9]

The relationship between BRAF V600E mutation and gender is shown by different findings among several researchers. Hong et al. found that BRAF V600E mutation tends to be found in females with irregular tumor shapes, but Zhang et al.'s study did not find a relationship between BRAF V600E mutation and gender at diagnosis.[8,16] Most studies agreed that BRAF V600E mutation was associated with older age at tumor diagnosis. Still, two studies by Gao et al. and Bandoh et al. did not find an association between this mutation and age at diagnosis.[12,13,18–21] Several studies have linked tumor size to BRAF mutations. One study by Shi et al. found BRAF mutations to be associated with larger tumor sizes, but most other studies contradict this finding and found BRAF mutations were found in patients with smaller tumor sizes compared to PTC without mutations.[14]

Most studies have mentioned the association of BRAF V600E mutation with invasive and metastatic histopathological features such as capsule invasion, extrathyroid, vascular, nerve, and lymph node metastasis. Bandoh et al. found BRAF mutation associated with tracheal invasion and bilateral neck lymph node metastasis.[21] Only 1 study, namely Zhang et al., found no association between BRAF mutations and capsule, lymphatic, vascular, nerve invasion, and neck lymph node metastasis.[16] What is interesting is that if PTC with BRAF mutations occurs together with Hashimoto's thyroiditis, the incidence of lymph node metastasis is found to be lower with a smaller tumor size.[15,16] This may be due to the autoimmune condition of Hashimoto's thyroiditis, which can change the molecular profile of PTC. Some researchers believe that Hashimoto's thyroiditis can develop into PTC, and many studies have found that the relationship between these two conditions that occur together is very close. It is currently believed that Hashimoto's thyroiditis is one of the risk factors in the pathogenesis of PTC that can cause PTC by mediating RET/PTC gene recombination and affecting gene transcription regulation.[15] Most literature associates BRAF mutation with higher recurrence and lower survival in PTC. However, one study by Al-Masri et al. found no significant association between BRAF V600E mutation and disease-free survival and overall survival.[22]

Several changes in the research designs that could impact the comparability of the findings, such as changes in the populations examined and the techniques employed to identify mutations and evaluate phenotypic traits, are among the study's limitations. It is challenging to determine the overall effect of the BRAF V600E mutation on thyroid cancer since different research has produced contradictory findings about the relationship between the mutation and different phenotypic traits. Limited sample sizes in several research could impact how broadly the findings can be applied. Since

papers with significant findings are more likely to be published than those with null results, this systematic review could be skewed by publication bias.

These drawbacks emphasize the necessity of additional research employing consistent and defined methods for identifying BRAF V600E mutations (such as NGS) and comparable standards for assessing tumor attributes to enhance study comparability. Future research should also concentrate on bigger sample sizes with different populations to better understand the genetic and environmental factors influencing the phenotypic expression of BRAF V600E mutations. The development of thyroid cancer linked to BRAF V600E mutations, as well as its long-term clinical implications and any changes in tumor features, will be better understood through longitudinal studies that track patients over time. Future research should also investigate the underlying molecular processes by which BRAF V600E mutations affect tumor behavior. This might involve research on the MAPK pathway and how it affects.

CONCLUSION

BRAF V600E mutation significantly affects the phenotypic characteristics of thyroid cancer, especially PTC type. This mutation is associated with several aggressive characteristics including increased risk of invasion and metastasis which increases the risk of local and distant recurrence. This mutation is more frequent in the tall-cell variant of PTC, a more aggressive subtype. BRAF V600E mutation is also often associated with cancer at a more advanced clinical stage. Increased expression of the aggressive phenotype of this mutation is associated with worse prognosis and decreased survival in PTC patients especially those who also have additional mutations or aggressive molecular markers. Overall, BRAF V600E mutation in thyroid cancer serves as an important biomarker that can be used to predict the clinical behavior of cancer, including tumor aggressiveness and risk of metastasis. Detection of this mutation can be an important consideration in determining more appropriate management and treatment in thyroid cancer patients

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