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## REVIEW/DERLEME

# Prevalence of BRAF Mutation in Papillary Thyroid Cancer

## Papiller Tiroid Kanserinde BRAF Mutasyonu Prevalansı

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**Abstract**
**Objectives:** Papillary thyroid cancer (PTC) is the most common endocrine malignancy and the most common genetic anomaly with PTC is the BRAF V600E mutation. This mutation is linked to many clinical and pathological features and may have a diagnostic and therapeutic role especially in the era of targeted therapy. The aim of this study is to review the prevalence of BRAF V600E mutation in PTC, its distribution according to the histological subtype and geographic area and its association with the age of patients, gender, subtype and recurrence of tumors.
**Methods:** The Pubmed database was searched to look for articles about BRAF mutation in PTC. Outcomes of interest included prevalence, age, gender, country, subtype and recurrence.
**Results:** The prevalence of BRAF V600E mutation in PTC was 47%, with noticeably higher prevalence in the eastern countries. The prevalence of BRAF V600E was also higher in the tall and classic subtypes and could be associated with worse prognosis and higher risk of recurrence.
**Conclusions:** The BRAF mutation, which is more prevalent in the eastern countries, is determined to be an important molecular marker for PTC.
**Key words:** Papillary thyroid cancer, BRAF mutation, prevalence

**Özet**
**Amaç:** Papiller tiroid kanseri (PTK) en sık endokrin malignite olup PTK ile ilişkili en sık genetik anomali BRAF V600E mutasyonudur. Bu mutasyon birçok klinik ve patolojik özellikler ile ilintilidir ve özellikle hedefe yönelik tedavi çağında tanısal ve tedavisel rolü olabilir. Bu çalışmanın amacı, BRAF V600E mutasyonunun PTK için prevalansını, histolojik varyant ve coğrafi bölgeye göre dağılımını, hasta yaşı, cinsi, tümör alt tipi ve nüksü ile olan ilişkisini değerlendirmektir.
**Yöntemler:** PubMed veritabanında PTK için BRAF mutasyonu ile ilgili makaleler taranarak prevalans, yaş, cins, ülke, alt tip ve nüksü içeren veriler değerlendirildi.
**Bulgular:** Doğu ülkelerinde belirgin olarak daha yüksek olmak üzere PTK için BRAF V600E mutasyonunun prevalansı %47 saptandı. Daha kötü prognoz ve daha yüksek nüks riski ile ilişkili olabilecek şekilde BRAV V600E prevalansı, *tall* hücre varyantı ve klasik varyantta daha yüksekti.
**Sonuç:** Doğu ülkelerinde PTK için daha yüksek prevalansa sahip olduğu saptanan BRAF mutasyonunun, bu malignite için önemli bir moleküler belirteç olduğu düşünülmektedir.
**Anahtar kelimeler:** Papiller tiroid kanseri, BRAF mutasyonu, prevalans

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## INTRODUCTION

Thyroid cancer, with a rapidly increasing incidence, is the most common endocrine malignancy, which accounts for 1% of all cancers [1]. Papillary thyroid cancer (PTC) accounts for around 85% of all thyroid malignancies [2]. Although it has a favorable prognosis with an average 10-year survival rate of more than 95%, approximately 10% of patients eventually die mainly because of disease recurrence [3].

Recent advances in molecular medicine have led to significant insights into the genetic basis of thyroid tumorigenesis, and a large number of genetic mutations were found to be involved in the carcinogenesis of PTC, like; BRAF, RAS, RET, PAX8 genes mutations and others, which may carry diagnostic, prognostic and therapeutic roles [4].

BRAF gene is located on chromosome 7, and it encodes the BRAF protein, which is involved in a pathway that controls and regulates many cellular processes, like; cellular proliferation, differentiation and apoptosis. Mutations in this gene predispose the patients to different diseases and malignancies, and PTC is a well-known example, in which BRAF mutations are the most commonly observed mutations. The most common mutational hotspot is BRAF V600E, which creates a constitutively active BRAF kinase that has been proven to be an oncogene in human cancer [5-7].

This mutation has been the subject of intensive investigations because of its specificity for PTC. It is not frequently seen in follicular, Hurthle cell, and medullary carcinomas, and importantly, BRAF mutation is not present in benign tumors [8].

In addition to that, this mutation represents a valuable marker that could be used preoperatively to estimate the risk of PTC recurrence, which may help us to give an individualized treatment [9,10]. Additionally, this mutation has been found to confer a worse prognosis for PTC due to its association with advanced and more aggressive presentation and subtypes and decreased response to radioactive iodine treatment [11].

Many different studies were held worldwide to study the prevalence of the BRAF mutation in PTC and its association with the clinical and pathological features as well as its role in the diagnosis of thyroid cancer especially if the FNA and cytology of a nodule yields a result as "indeterminate" such as in the Bethesda 3, 4 and 5 categories.

We performed this systemic review in order to review the prevalence of the BRAF mutation in PTC, its association with the geographic areas and its relationship to age, gender, subtype and recurrence.

## METHODS

A comprehensive search of the articles evaluating the prevalence of BRAF-V600E mutation in PTC was performed. We searched the PubMed database using the terms: “BRAF”, “B-RAF”, “papillary thyroid carcinoma”, “papillary thyroid cancer”, “PTC” in different combinations to identify relevant publications.

Outcomes of interest were: prevalence, age, gender, geographic area, subtype and recurrence. We initially narrowed our search based on the titles of the articles followed by abstracts and finally full-text articles were reviewed.

The search was limited to human studies. All articles were written in the English language. The references of the eligible articles were checked for relevant studies.

## RESULTS

### Prevalence of BRAF in PTC

In general, the prevalence of BRAF mutation in our review was 47.3% (Table 1).

#### The association between BRAF mutation and age

The correlation between patient's age and BRAF mutation has been the subject of considerable controversy.

**Table 1:** The prevalence of BRAF mutation in PTC in the current literature

| Study | Number of patients | Number of BRAF(+) patients | Percentage of BRAF(+) patients |
|---|---|---|---|
| Gallupini 2016 [37] | 185 | 115 | 62% |
| Jo 2016 [32] | 161 | 102 | 63.3% |
| DeBiase 2014 [38] | 155 | 85 | 54.8% |
| Li 2013 [27] | 388 | 297 | 76.5% |
| Xing 2013 [25] | 1849 | 845 | 45.7% |
| Schulten 2012 [12] | 115 | 72 | 62.6% |
| Basolo 2010 [16] | 1060 | 437 | 44.6% |
| Sykrova 2010 [39] | 242 | 81 | 33.4 % |
| O'Neill, 2010 [40] | 101 | 60 | 59.4% |
| Musholt 2010 [41] | 290 | 120 | 48.6% |
| Xing 2009 [42] | 100 | 40 | 40% |
| Abu baker 2008 [43] | 296 | 153 | 51.7% |
| Elisei 2008 [14] | 102 | 38 | 37.3% |
| Lupi 2007 [17] | 500 | 214 | 42.8% |
| Fugazzola 2006 [44] | 260 | 99 | 38% |
| Riesco-Eizaguirre 2006 [18] | 67 | 28 | 41.7% |
| Nikiforova 2003 [13] | 119 | 45 | 37.8% |
| **Total** | **5990** | **2832** | **47.3%** |

Schulten et al observed that BRAF-negative patients were 7 years younger than the BRAF-positive patients as the mean age of BRAF-positive patients was around 44 years while the mean age of BRAF-negatives was around 37 years (p = 0.025) [12]. Nikiforova et al reported that BRAF mutation was associated with older age, where they found that the mean age of BRAF-positive patients was 49 years while the mean age of BRAF-negative patients was 35 years [13]. Similarly, an Italian study found that the BRAFV600E mutation was significantly more prevalent in older patients, in particular, in those older than 60 years (p=0.02) [14]. This result is consistent with the finding that an advanced age at diagnosis is associated with poor prognosis [15].

In contrast, Basolo et al observed an inverse association between age at the time of diagnosis and BRAF mutation as they found that this mutation was more common in younger patients (p=0.006) and the mean age of BRAF-positive patients was 43 years, whereas the mean age of BRAF-negative patients was around 46 years [16].

But many other investigators did not reveal any significant association between BRAF mutation and age [17-19-21]. For example, in a large meta-analyses that included 1168 patients, no association was determined between age and the BRAF mutation, and another meta-analysis that included 3437 patients also supported this finding [22].

## Association between BRAF mutation and gender

While there was considerable controversy regarding the relationship between age and the presence of BRAF mutation, almost all of the studies stated that there is no significant association between the presence of BRAF mutation and gender [13,17,18,20-22]. Except for few studies like the one of Xu et al, which reported significant difference in the distribution of BRAF mutation between males and females with higher prevalence of this mutation in males ($p<0.05$) [23].

## Association between BRAF mutation and the geographic area

It was found that there is significant geographic difference in the prevalence of BRAF mutation, with higher prevalence in the Asian countries especially Korea which exhibits the highest rate of BRAF mutation and lower prevalence in the west [6].

This observation is supported by many different studies. For example; according to Kim et al, the prevalence of BRAF in PTC mutation among Korean patients was around 83% [24]. And in another retrospective study that involved 1849 patients, the prevalence of BRAF mutation in PTC was found to be around 67% in Japan, 46% in the USA, 55% in Italy and

42% in Poland [25]. Most of the studies supported these differences (Table 2).

**Table 2:** The prevalence of BRAF mutation according to the countries

| Study | Country | Number of patients | Percentage of BRAF(+) patients |
|---|---|---|---|
| Jo 2016 [32] | Korea | 161 | 63.4% |
| Kim 2015 [24] | Korea | 3019 | 82.7% |
| DeBiase 2014 [38] | Italy | 155 | 54.8% |
| Hong 2014 [40] | Korea | 2431 | 73.7% |
| Xing 2013 [25] | Japan | 49 | 67.4% |
| Xing 2013 [25] | USA | 691 | 45.7% |
| Xing 2013 [25] | Poland | 99 | 42% |
| Kurtulmus 2012 [45] | Turkey | 109 | 39.4% |
| Schulten 2012 [12] | Saudi Arabia | 115 | 63% |
| Sykrova 2010 [39] | Czech Republic | 242 | 33.5% |
| Guan 2009 [47] | China | 1023 | 61.6% |
| Elisei 2008 [14] | Italy | 102 | 37.3% |
| Riesco-Eizaguirre 2006 [18] | Spain | 67 | 74.1% |
| Fugazzola 2006 [44] | Italy | 260 | 38% |
| Xing 2005 [21] | Ukraine | 29 | 55% |

## The prevalence of BRAF mutation over time

The prevalence of this mutation has changed over time. A recent publication revealed an increase in the prevalence of BRAF mutation in thyroid malignancies from 62% to 74% in the last 20 years in Korea. Similarly, in the United States, the overall prevalence of BRAF mutations has increased in the last 40 years [6]. The definitive cause behind this is still unknown, but it may be attributed to the improvement in the modalities that detect BRAF mutation and small PTCs.

## Association between BRAF mutation and the PTC subtypes

The prevalence of BRAF V600E mutation differs according to the histological subtypes of PTC, with significantly higher prevalence in the conventional and tall variants, and lower prevalence in the follicular subtype [26]. To make things more clear, in a recent study, the prevalence of BRAF mutation was found to be 88% in the tall variant, 80% in the classical variant and around 40% in the follicular variant [27]. Basolo et al stated that, around 80% of tall cell variant PTCs were mutated, 70% of classic variants and only 21% of follicular variants harbored BRAF mutation [16]. In other studies, BRAF mutation was significantly associated with the tall cell variant ($p<0.05$), and BRAF-negative tumors were associated with the follicular variant [13,18].

Similarly, Lupi et al reported that the highest frequency of BRAF V600E was found in the tall variant (80%), followed by the conventional variant (68%), and as expected, significantly lower frequency (19%) of BRAF V600E mutations was observed in the follicular variant [17]. Similarly, Lee et al found that the prevalence of BRAF mutation was around 80% in the tall subtype, 60% in the conventional subtype and 17% in the follicular subtype [20].

## Association between BRAF mutation and recurrence

It was found that there is a significant association between BRAF mutation and PTC recurrence, disease recurrence occurred in 32% of BRAF-positive patients but only 7.6% of BRAF-negative patients developed recurrence ($p=0.02$) [18]. In a study that included 2099 patients, BRAF-positive patients were two times more likely to develop recurrence in the future (21% vs 11%) [28].

According to Xing et al, the association between BRAF mutation and disease recurrence remained significant even after eliminating the effect of poor prognostic factors, like; lymph node metastasis, extra-capsular and advanced stage ($p=0.03$). As mentioned before, tall-cell variant PTCs have a more aggressive course, to eliminate the effect of this factor some studies tried to find the association between tumor recurrence and BRAF mutation using non-tall cell tumors, and the association remained significant in the remainder of the tumors ($p=0.02$). This demonstrates that BRAF

mutation is an independent predictor of a more aggressive disease with worse prognosis [21].
Noticeably, BRAF mutation was more common in the recurrent tumors (85% of recurrent tumors harbored BRAF mutation, while only 65% of primary tumors were BRAF-positive) emphasizing that it is the major mutation in recurrent PTC [29,30].

## DISCUSSION

Thyroid cancer is the most common endocrine malignancy, it accounts for 1% of all malignancies, and it was found to be more common in the Arab world where its incidence reaches 6% of all malignancies [1,12].
PTC accounts for 85% of all thyroid malignancies [2]. Although PTC is considered to be a curable disease with a 10-year-survival rate of more than 90%, disease recurrence is quite common, and a minority of patients with recurrent disease dies. Those patients with higher risk of recurrence, or when a more aggressive disease is expected need to be identified for appropriately more aggressive treatment to reduce the related morbidity and mortality. Clinical decisions regarding those patients depends on clinical and pathological criteria, these criteria are not very accurate, making it a challenging task to stratify patients with PTC for optimal treatment. This fact paved the road to the world of molecular biology and the use of molecular markers. BRAF V600E mutation is the most common mutation in PTC, and has emerged as a promising molecular marker for better prognostication and risk stratification [28,31].
The BRAF V600E mutation is specific for PTC, is not seen in benign tumors, is uncommon in follicular thyroid cancer (<1.4%), and is not frequently seen in Hurtle and medullary thyroid carcinomas, but it was detected in the anaplastic thyroid carcinoma (10%) [8,13,32,33].
Interestingly, the prevalence of BRAF mutation was found to be associated with the geographic area with a significantly higher prevalence in Asia, especially Korea where the prevalence of BRAF mutation reaches 83%, and lower prevalence in the west [6,24]. Although the mechanisms underlying this difference in BRAF mutation frequencies are not well understood, a recent theory suggested that these differences might be associated with higher iodine intake in Asian populations.
Furthermore, Hashimoto's thyroiditis is strongly associated with the development of PTC. Because the prevalence of Hashimoto's thyroiditis is higher in Korea, this positive correlation may provide an explanation for the higher incidence of PTC in this country [6].
While geographic differences in the incidence of BRAF mutations are well established, the association between age and BRAF mutation is still controversial. Most of the studies denied the presence of significant association, while some studies reported that BRAF mutation was associated with older age and they stated that it is one of the reasons behind the worse prognosis of PTC in the elder patients, and few studies found an inverse relationship between age and the BRAF mutation. As a matter of fact, BRAF V600E mutation is very uncommon in childhood PTC [34].
Most of the studies reported no significant difference according to gender. Except for a few studies that found higher prevalence of BRAF mutations in males correlated with worsened prognosis of PTC [20,23].
PTC can be classified into several subtypes as the most common ones are: conventional, follicular variant and tall cell variant [35]. The prevalence of BRAF V600E mutation differs according to subtype, with significantly higher prevalence in the tall variant (>80%) and conventional variant (70%) and lower prevalence in the follicular subtype [13,16-18,20,26,27]. Some researchers tried to correlate this finding to the aggressiveness and prognosis of the disease where they found that the classic subtype has less aggressive course than age- and size- matched tall-cell PTC in which BRAF mutation was more common. For

example, lymph node metastasis, advanced stage and recurrence are more common in tall than classic variant, and much less common in the follicular variant [21,36].

Moreover, most of the anaplastic thyroid cancers and the poorly differentiated tumors that were BRAF-positive were found to have adjacent areas of tall-cell variant PTC. These findings provide evidence for the association between this mutation and aggressive tumor course which makes it a potentially important marker for tumor diagnosis and prognosis and for directing a more appropriate treatment [13].

Death in PTC is strongly linked to disease recurrence. Most tumor recurrences occur in the thyroid site, para-tracheal and cervical areas. There are many studies that correlate the association between recurrence and the BRAF mutation. Most of the studies demonstrated higher risk of recurrence in patients with BRAF mutation even after adjustment for other factors that worsen the prognosis [21]. In addition to that, BRAF-positive tumors are more likely to be less differentiated with poor response to radioiodine treatment, and it was observed that the uptake of $^{131}I$ was absent in the majority of BRAF-positive tumors [18].

Interestingly, BRAF mutation was found to be more common in recurrent tumors, which reveals that this is the major mutation in recurrent PTC [29-30].

## CONCLUSIONS

BRAF mutation is the most common mutation in PTC with higher prevalence in the eastern countries of the world. It is a potentially useful molecular marker, and may have a role in the risk stratification, prognosis and treatment of PTC. More studies should be done in order to confirm its benefits for the diagnosis, treatment and surveillance of PTC.

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