

Review Article

BRAF mutation in papillary thyroid cancer: a meta-analysis

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Received March 7, 2016; Accepted June 5, 2016; Epub July 15, 2016; Published July 30, 2016

Abstract: Background: The role of the BRAF V600E mutation as an independent prognostic factors in papillary thyroid cancer (PTC) has not been fully quantified. To address this controversy, a meta-analysis was performed to determine the strength of associations between BRAF mutation status and PTC prognosis, focusing on the recurrence or persistence of the PTC. Review Methods: PubMed, Web of Knowledge, Ovid's database were searched from January 2000 to August 2015. 236 relevant studies were hand-searched. We selected 30 studies that included 5873 PTC patients and calculated the pooled odds ratios (ORs) with 95% confidence intervals (CIs) for each study. Results: In 30 studies, compared with the patients who had the wild-type BRAF genes, the PTC patients with the BRAF V600E mutation had increased ORs of an older age (≥ 45 years) (OR, 1.51; 95% CI, 1.17-1.94), an extrathyroidal invasion (OR, 2.03; 95% CI, 1.76-2.34), a lymph node metastasis (OR, 1.59; 95% CI, 1.40-1.81), an advanced TNM stage (OR, 1.77; 95% CI, 1.56-2.01). The BRAF mutation in PTC was not associated with multiplicity (OR, 1.06; 95% CI, 0.91-1.23) or distant metastasis (OR, 0.88; 95% CI, 0.55-1.42). In 8 studies, patients with the mutation had 3.34-fold increased risk of recurrent and persistent disease (95% CI, 2.36-4.73). The associations were generally consistent across the different study populations. Conclusion: This meta-analysis demonstrates that the BRAF V600E mutation in PTC was significantly associated with PTC older age, extrathyroidal extension, lymph node metastasis, advanced stage AJCC III/IV and recurrence. We recommend that patients with a suspected malignant thyroid nodule undergo preoperative BRAF V600E testing to guide the initial surgical treatment in PTC.

Keywords: BRAF, papillary thyroid carcinoma, meta-analysis

Introduction

Papillary thyroid carcinoma (PTC) is the most usual endocrine malignancy [1]. The increasing incidence of thyroid cancer, especially PTC has been observed worldwide [2-4]. The prognosis in PTC with 10-year survival rates is approximately 80-90% [5]. But 10-15% patients suffer from local or distant recurrences [6-8]. Several studies have found a close relationship between BRAF mutation and aggressive clinicopathologic characteristics of PTC, including extrathyroidal extension, lymph node metastasis, histologic subtypes, and advanced disease stages, as well as disease recurrence/persistence [9-12]. However, some authors indicated that this mutation was not associated with poor clinical outcome or with pathologic aggressiveness [13-16]. The clinical significance of BRAF mutation in PTC was still controversial.

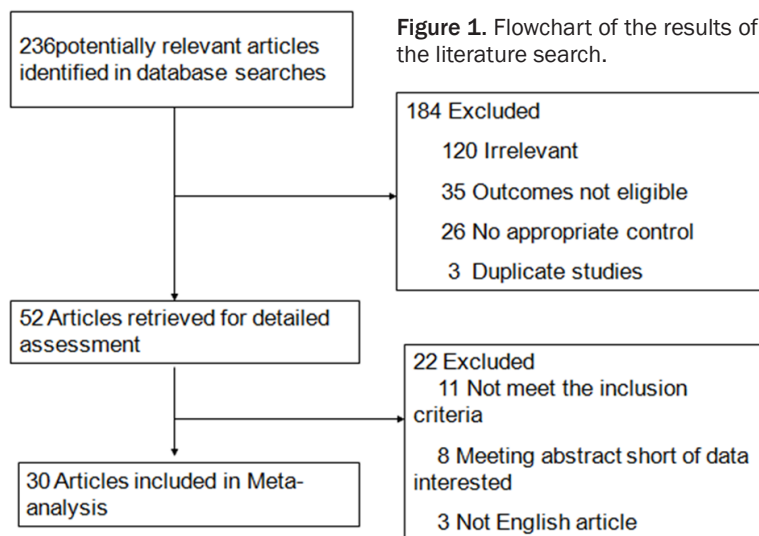
In our study, we performed a comprehensive meta-analysis to clarify the associations of the BRAF mutation with clinicopathological features and prognosis.

Materials and methods

Selection criteria and search strategy

We conducted an electronic search of the papers in the Medline database, the Web of Knowledge from January 2003 to August 2015. The search was restricted to English language publications. Search term combinations were "BRAF", "papillary thyroid cancer", and "PTC". All of the reference lists from the main reports and relevant reviews were checked for additional eligible studies. The relevant unpublished data that were presented at international meetings were also included.

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We analyzed data extracted from these articles for the presence of following features: recurrence/persistence, age, multiple nodules, extrathyroidal extension, lymph node metastasis, distant metastasis, and clinical AJCC stage. We also explored the BRAF expression rate, the study design, year, country, treatment protocol, and criteria for defining recurrent/persistent disease.

Statistical analysis

A formal meta-analysis was made for all studies. Odds ratios (ORs) and the 95% confidence intervals (CIs) for each study were generated by inputting number of BRAF mutation in case group, total number of case group, number of BRAF mutation in control group and total number of control group into the RevMan. Pooled estimates of the complications were calculated using a fixed-effects model, but a random-effects model was used according to heterogeneity. The test of effect homogeneity was performed using χ^2 tests, with $P \leq 0.05$ indicating significant heterogeneity. When the hypothesis of homogeneity was not rejected, the fixed-effects model was used to estimate the pooled effect of the outcomes; when the reverse was true, the random-effects model was also calculated.

Results

Study selection

We identified 236 potentially relevant articles (**Figure 1**). After exclusion of duplicate refer-

ences, none-relevant literature, and those that did not satisfy inclusion criteria, 52 candidate articles were considered for the meta-analysis. After careful review of the full text of these articles, 30 studies were included. The study characteristics were summarized in **Table 1**. The publication dates ranged from 2000 to 2015.

Outcome measures

For patients with older age ≥ 45 years (**Figure 2**), the average OR from 11 studies was 1.51 (95% CI, 1.17-1.94).

The heterogeneity of the data was not significant ($P=0.11$), and the I^2 estimate of the variance between the studies was 36%. For the cases of lymph node metastasis (**Figure 3**), 24 studies were included in the meta-analysis. Despite the wide range of variance among the studies, the overall OR was 1.59 (95% CI, 1.40-1.81). The heterogeneity of the data was significant ($P=0.0001$), and the I^2 estimate of the variance between the studies was 59%. For the presence of multiplicity (**Figure 4**), the average OR from 17 studies was 1.06 (95% CI, 0.91-1.23). The heterogeneity of the data was not significant ($P=0.54$), and the I^2 estimate of the variance between the studies was 0%. For extrathyroidal invasions (**Figure 5**), the average OR from 21 studies was 2.03 (95% CI, 1.76-2.34). The heterogeneity of the data was significant ($P<0.00001$), and the I^2 estimate of the variance between the studies was 72%. For the presence of distant metastasis (**Figure 6**), the average OR from 11 studies was 0.88 (95% CI, 0.55-1.42). The heterogeneity of the data was not significant ($P=0.31$), and the I^2 estimate of the variance between the studies was 14%. For the presence of an advanced TNM stage (**Figure 7**), the overall OR from 25 studies was 1.77 (95% CI, 1.56-2.01). The chi-square test and I^2 test of heterogeneity revealed a considerable level of heterogeneity in the risk estimates ($P<0.0001$, $I^2=63\%$).

For recurrent and persistent disease (**Figure 8**), 8 studies were initially included in the meta-analysis. Heterogeneity was not present

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Table 1. Overview of the reviewed studies

Author, Year	Country	No. of patients	Sex (male/female)	Patient source	Mean age, years	BRAF mutation rate (%)
Liu 2014 [17]	China	132	29/113	The First Affiliated Hospital of Xi'an Jiaotong University	P: 40.57 N: 39.25	60.61
Park 2014 [18]	Korea	688	135/553	Gangnam Severance Hospital	P: 45.2 N: 45.4	69.2
Henke 2015 [19]	USA	508	125/383	Washington University School of Medicine	P: 45.5 N: 45.1	66.9
Schulten 2015 [20]	Saudi Arabia	25	7/18	King Abdulaziz University Hospital	P: 45.9 N: 30.9	56
He 2014 [21]	China	187	28/159	Anhui Medical University	42.57	63.64
Czarniecka 2015 [22]	Poland	233	29/209	M. Sklodowska-Curie Memorial Institute	P: 51.1 N: 42.0	54.5
Howell 2011 [23]	USA	219	—	University of Pittsburgh,	—	39.27
Xing 2005 [24]	USA	219	58/161	The Johns Hopkins University School	P: 43 N: 45	48.9
Xing 2009 [25]	USA	190	53/137	The Johns Hopkins University School	—	38.4
Elisei 2008 [26]	Italy	102	20/82	The University Hospital of Pisa	P: 45.9 N: 41.0	37.3
O'Neill 2010 [27]	Australia	101	19/82	Royal North Shore Hospital	61.7	59
Abubaker 2007 [28]	Saudi Arabia	296	73/223	The King Faisal Specialist Hospital and Research Centre	—	48.3
Fugazzola 2006 [29]	Italy	260	79/190	University of Milan and Fondazione Policlinico	P: 42 N: 39	38
Sapio 2006 [30]	Italy	43	5/32	the University of Naples	P: 40.2 N: 43.1	44.2
Yip 2009 [31]	USA	206	49/157	University of Pittsburgh School of Medicine	P: 51.9 N: 49.4	51.5
Kim 2006 [32]	Korea	203	35/168	University of Ulsan College of Medicine	P: 44 N: 43	73.4
Riesco-Eizaguirre 2006 [33]	Spain	67	12/55	Hospital Universitario La Paz	—	41.7
Guan 2009 [34]	China	1032	—	The First Affiliated Hospital of China Medical University	—	62
Goutas 2007 [35]	Greece	55	10/45	University of Athens	43.5	27.3
Lee 2006 [36]	Australasia	100	10/90	Royal College of Pathologists	P: 49.4 N: 46.7	58
Ito 2009 [37]	Japan	631	67/564	Kuma hospital	P: 50.6 N: 50.2	38.4
Fugazzola 2004 [38]	Italy	56	11/36	University of Milan	—	32.1
Durante 2007 [39]	Italy	93	27/66	University of Rome	P: 53.4 N: 43.9	60.2
Namba 2003 [40]	Japan	126	30/96	Nagasaki University Graduate School	—	30.2
Nakayama 2007 [41]	Japan	40	11/29	Yokohama City University Hospital	P: 57.4 N: 43.1	65
Abrosimov 2006 [42]	Japan	40	6/34	Nagasaki University Graduate School	P: 52.1 N: 39.5	57.5
Jo 2006 [43]	Korea	161	27/134	Chungnam National University School of Medicine	P: 45.1 N: 44.2	63.4
Rivera 2010 [44]	USA	—	—	Memorial Sloan-Kettering Cancer Center	—	—
Kim 2005 [45]	Korea	79	11/68	Eulji University School of Medicine	—	81.0
Liu 2005 [46]	China	101	30/71	National Sun Yat-Sen University	—	46.5

P: Positive, N: Negative.

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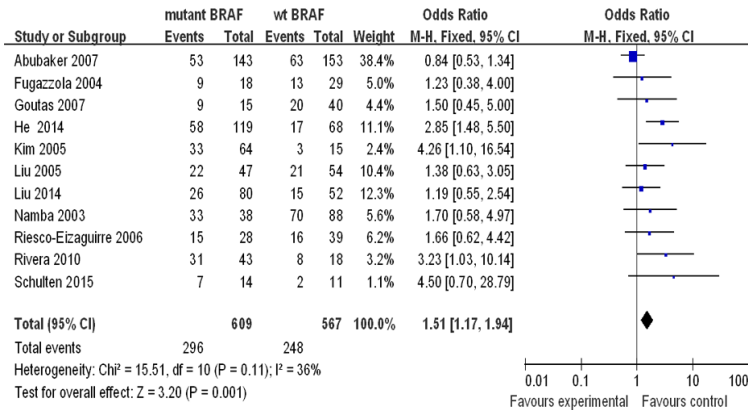


Figure 2. Fixed effect model of the odds ratios (ORs) with 95% confidence intervals (CIs) of the patients age ≥ 45 years associated with the BRAF V600E mutation is shown.

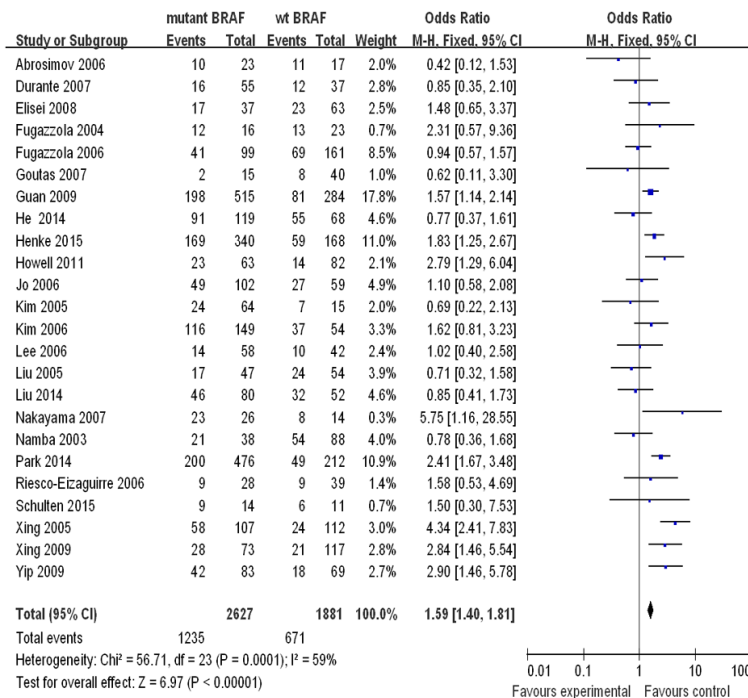


Figure 3. Random effect model of the odds ratios (ORs) with 95% confidence intervals (CIs) of the presence of lymph node metastasis associated with the BRAF V600E mutation is shown.

($P=0.84$, $I^2=0\%$). The overall OR of developing recurrent and persistent disease from the 8 studies including 1312 follow-up cases was 3.34 (95% CI, 2.36-4.73).

Discussion

The BRAF mutation was detected over 40 malignant neoplasm, of which the BRAF V600E

mutation was more than 90% [47]. In our study, we demonstrated that the BRAF V600E mutation of PTC was related to the clinicopathological features of PTC and poor clinical outcome. To evaluate the strength of association of the BRAF V600E mutation with adverse clinical and pathological outcomes, we performed a meta-analysis of 30 studies which evaluated 5873 patients.

Within the studies included, the highest BRAF mutation rate was 81.0% in a study conducted in the Korean reported by Kim et al [45]. The lowest mutation rate was 27.3% in a study completed in Greece by Goutas et al [35]. The BRAF V600E mutation rate was significantly different between these two studies, which may be attributable to the different ethnicities of the study populations.

This meta-analysis revealed that the BRAF mutation was significantly associated with older age, advanced TNM stage, extrathyroidal invasion, lymph node metastasis, which was consistent with previous reports [48, 49]. The results presented here alert surgeons to patients that may be at increased risk of carrying a BRAF mutant tumor as the focus for screening. No correlation was found between BRAF mutation and the presence of multiplicity and the presence of distant metastasis in clinical staging systems.

Several mechanisms are involved in the aggressive phenotype of PTC that is promoted by the BRAF mutation [50]. The activating mutation is located in exon 15 of the B isoform of the Raf kinase gene, which results in a constitutive activated state of kinase activity and promotes

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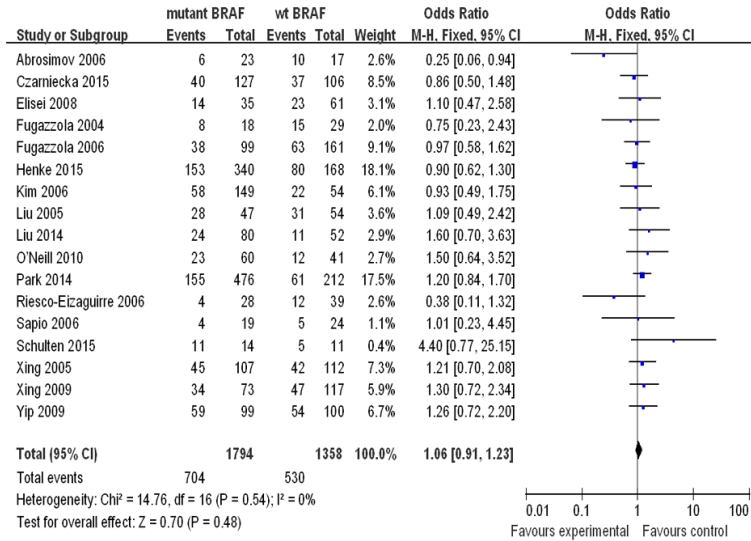


Figure 4. Fixed effect model of the odds ratios (ORs) with 95% confidence intervals (CIs) of the presence of multiplicity associated with the BRAF V600E mutation is shown.

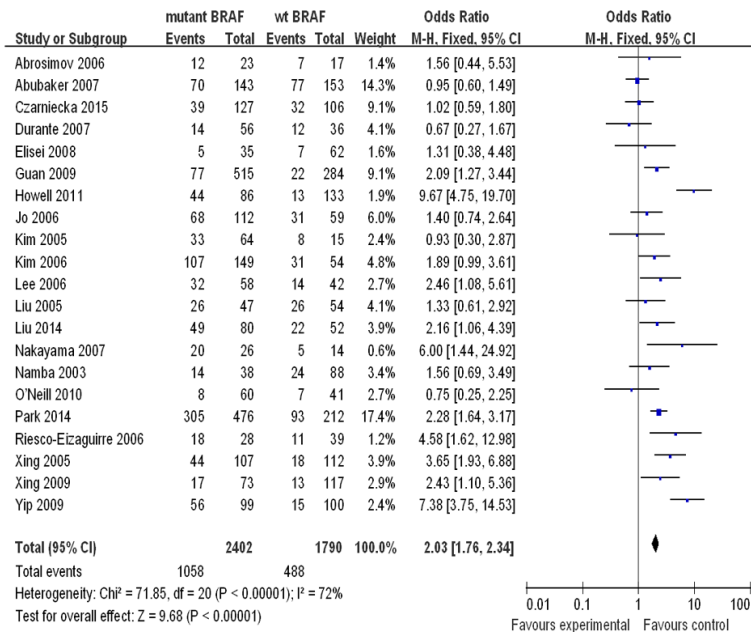


Figure 5. Random effect model of the odds ratios (ORs) with 95% confidence intervals (CIs) of the presence of an extrathyroidal invasion associated with the BRAF V600E mutation is shown.

tumorigenesis through the mitogen-activated protein kinase (MAPK) pathway [51]. The expression of RAS, BRAF and phosphorylated MEK, in papillary thyroid cancer is higher than benign tissues. The expression of phosphorylated ERK in nuclear was increased and the RAS-BRAF-MEK-ERK signaling pathway may be activated in PTC [52].

There are some limitations in our meta-analysis. Firstly, we did not evaluate the methods used to detect BRAF mutations for lacking data, which may affect the results. Secondly, we did not collect data on the treatment and clinical outcomes to analyze effect of the BRAF mutation on overall clinical outcome. Nevertheless, this study still reports some important and significant findings.

In conclusion, the meta-analysis confirmed that the BRAF mutation in PTC was correlated with high-risk clinicopathological factors and poor clinical outcome. The results obtained here suggest that the BRAF mutation should be considered a poor prognostic marker in PTC, and that BRAF mutational analysis may lead to better management for individual PTC patients.

Conclusions

This meta-analysis demonstrated that BRAF mutation was significantly correlated with adverse pathological features of PTC and could be considered as a poor prognostic marker for PTC.

Disclosure of conflict of interest

None.

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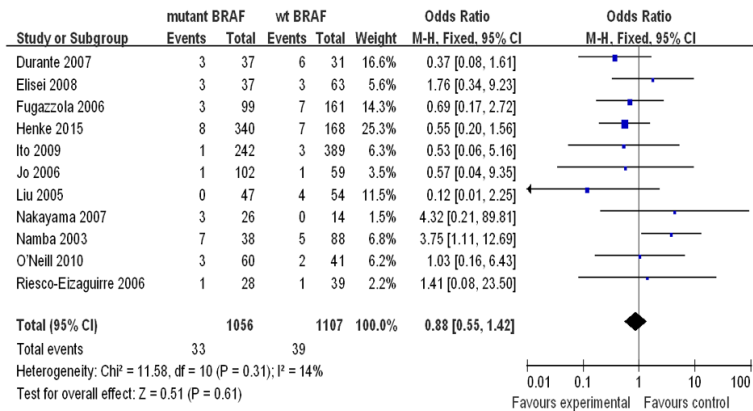


Figure 6. Fixed effect model of the odds ratios (ORs) with 95% confidence intervals (CIs) of the presence of distant metastasis associated with the BRAF V600E mutation is shown.

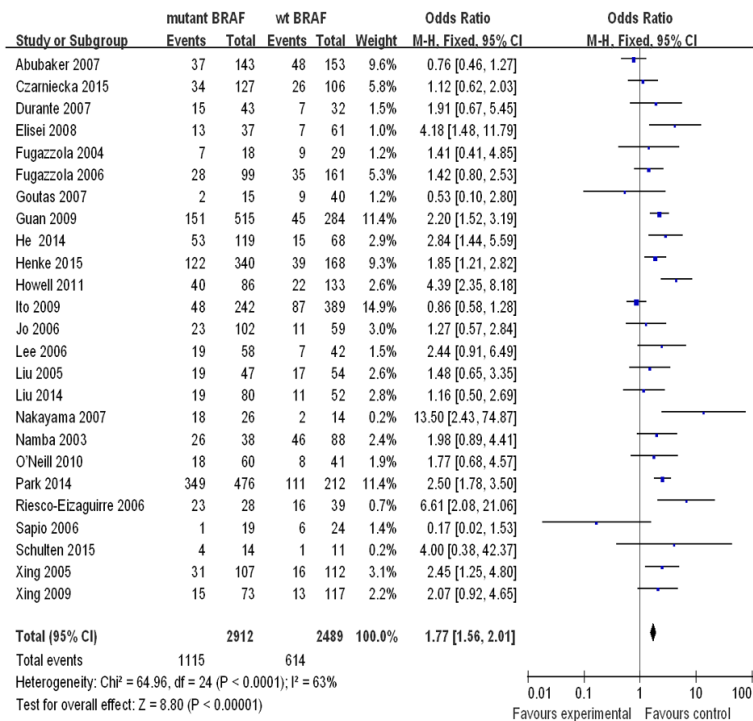


Figure 7. Random effect model of the odds ratios (ORs) with 95% confidence intervals (CIs) of the presence of an advanced stage (III and IV) associated with the BRAF V600E mutation is shown.

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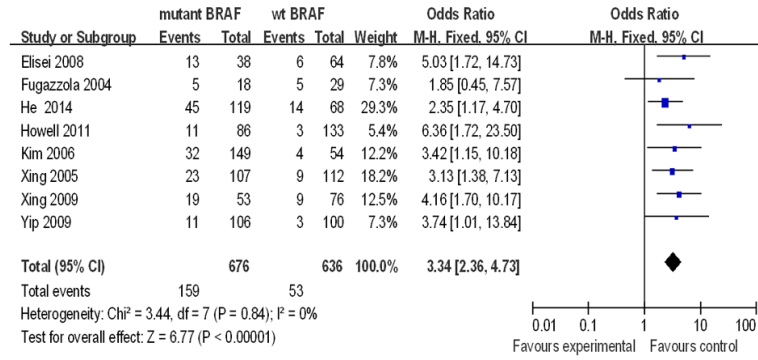


Figure 8. Fixed effect model of the risk ratios with 95% confidence intervals (CIs) of the recurrent and persistent disease associated with the BRAF V600E mutation is shown.

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