Review Article BRAF mutation in papillary thyroid cancer: a meta-analysis

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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 3.34fold increased risk of recurrent and persistent disease (95% Cl, 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.



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 randomeffects 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 fixedeffects 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 \geq 45 years (**Figure 2**), the average OR from 11 studies was 1.51 (95% Cl, 1.17-1.94).

The heterogeneity of the data was not significant (P=0.11), and the I² 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% Cl. 1.40-1.81). The heterogeneity of the data was significant (P=0.0001), and the I² 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% Cl, 0.91-1.23). The heterogeneity of the data was not significant (P=0.54), and the I² 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 I² 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 I² test of heterogeneity revealed a considerable level of heterogeneity in the risk estimates (P<0.0001, l²=63%).

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

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
0'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

Table 1. Overview of the reviewed studies

P: Positive, N: Negative.

	mutant BRAF wt BRAF			Odds Ratio	Odds Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	M-H, Fixed, 95% Cl	
Abubaker 2007	53	143	63	153	38.4%	0.84 [0.53, 1.34]	-	
Fugazzola 2004	9	18	13	29	5.0%	1.23 [0.38, 4.00]		
Goutas 2007	9	15	20	40	4.4%	1.50 [0.45, 5.00]		
He 2014	58	119	17	68	11.1%	2.85 [1.48, 5.50]		
Kim 2005	33	64	3	15	2.4%	4.26 [1.10, 16.54]		
Liu 2005	22	47	21	54	10.4%	1.38 [0.63, 3.05]		
Liu 2014	26	80	15	52	12.3%	1.19 [0.55, 2.54]		
Namba 2003	33	38	70	88	5.6%	1.70 [0.58, 4.97]		
Riesco-Eizaguirre 2006	15	28	16	39	6.2%	1.66 [0.62, 4.42]		
Rivera 2010	31	43	8	18	3.2%	3.23 [1.03, 10.14]		
Schulten 2015	7	14	2	11	1.1%	4.50 [0.70, 28.79]		
Total (95% CI)		609		567	100.0%	1.51 [1.17, 1.94]	•	
Total events	296		248					
Heterogeneity: Chi ² = 15.8	51, df = 10	(P = 0.1	1); l² = 36	5%				
Test for overall effect: Z =	3.20 (P =	0.001)		F	avours experimental Favours control			

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

	mutant I	BRAF	wt BR	AF		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	M-H, Fixed, 95% Cl
Abrosimov 2006	10	23	11	17	2.0%	0.42 [0.12, 1.53]	
Durante 2007	16	55	12	37	2.8%	0.85 [0.35, 2.10]	
Elisei 2008	17	37	23	63	2.5%	1.48 [0.65, 3.37]	+
Fugazzola 2004	12	16	13	23	0.7%	2.31 [0.57, 9.36]	
Fugazzola 2006	41	99	69	161	8.5%	0.94 [0.57, 1.57]	+
Goutas 2007	2	15	8	40	1.0%	0.62 [0.11, 3.30]	
Guan 2009	198	515	81	284	17.8%	1.57 [1.14, 2.14]	-
He 2014	91	119	55	68	4.6%	0.77 [0.37, 1.61]	
Henke 2015	169	340	59	168	11.0%	1.83 [1.25, 2.67]	-
Howell 2011	23	63	14	82	2.1%	2.79 [1.29, 6.04]	_
Jo 2006	49	102	27	59	4.9%	1.10 [0.58, 2.08]	+-
Kim 2005	24	64	7	15	2.0%	0.69 [0.22, 2.13]	
Kim 2006	116	149	37	54	3.3%	1.62 [0.81, 3.23]	+
Lee 2006	14	58	10	42	2.4%	1.02 [0.40, 2.58]	
Liu 2005	17	47	24	54	3.9%	0.71 [0.32, 1.58]	
Liu 2014	46	80	32	52	4.6%	0.85 [0.41, 1.73]	
Nakayama 2007	23	26	8	14	0.3%	5.75 [1.16, 28.55]	· · · · ·
Namba 2003	21	38	54	88	4.0%	0.78 [0.36, 1.68]	
Park 2014	200	476	49	212	10.9%	2.41 [1.67, 3.48]	-
Riesco-Eizaguirre 2006	9	28	9	39	1.4%	1.58 [0.53, 4.69]	
Schulten 2015	9	14	6	11	0.7%	1.50 [0.30, 7.53]	
Xing 2005	58	107	24	112	3.0%	4.34 [2.41, 7.83]	
Xing 2009	28	73	21	117	2.8%	2.84 [1.46, 5.54]	
Yip 2009	42	83	18	69	2.7%	2.90 [1.46, 5.78]	
Total (95% CI)		2627		1881	100.0%	1.59 [1.40, 1.81]	•
Total events	1235		671			_	
Heterogeneity: Chi ² = 56.	71, df = 23	(P = 0.0	001); l ² =	59%			
Test for overall effect: Z =	6.97 (P <	0.00001)			-	0.01 0.1 1 10 100
						F	avours experimental Favours control

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% Cl, 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

	mutant BRAF		wt BRAF		Odds Ratio		Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	M-H, Fixed, 95% CI
Abrosimov 2006	6	23	10	17	2.6%	0.25 [0.06, 0.94]	
Czarniecka 2015	40	127	37	106	8.5%	0.86 [0.50, 1.48]	-
Elisei 2008	14	35	23	61	3.1%	1.10 [0.47, 2.58]	
Fugazzola 2004	8	18	15	29	2.0%	0.75 [0.23, 2.43]	
Fugazzola 2006	38	99	63	161	9.1%	0.97 [0.58, 1.62]	+
Henke 2015	153	340	80	168	18.1%	0.90 [0.62, 1.30]	+
Kim 2006	58	149	22	54	6.1%	0.93 [0.49, 1.75]	+
Liu 2005	28	47	31	54	3.6%	1.09 [0.49, 2.42]	+-
Liu 2014	24	80	11	52	2.9%	1.60 [0.70, 3.63]	+
O'Neill 2010	23	60	12	41	2.7%	1.50 [0.64, 3.52]	
Park 2014	155	476	61	212	17.5%	1.20 [0.84, 1.70]	-
Riesco-Eizaguirre 2006	4	28	12	39	2.6%	0.38 [0.11, 1.32]	+
Sapio 2006	4	19	5	24	1.1%	1.01 [0.23, 4.45]	
Schulten 2015	11	14	5	11	0.4%	4.40 [0.77, 25.15]	
Xing 2005	45	107	42	112	7.3%	1.21 [0.70, 2.08]	
Xing 2009	34	73	47	117	5.9%	1.30 [0.72, 2.34]	+
Yip 2009	59	99	54	100	6.7%	1.26 [0.72, 2.20]	+
Total (95% CI)		1794		1358	100.0%	1.06 [0.91, 1.23]	•
Total events	704		530				
Heterogeneity: Chi ² = 14.	76, df = 16	(P = 0.5	4); ² = 0%	6			
Test for overall effect: Z =	0.70 (P =	0.48)				-	0.01 0.1 1 10 100
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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.

	mutant I	BRAF	RAF wt BRAF			Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	M-H, Fixed, 95% Cl
Abrosimov 2006	12	23	7	17	1.4%	1.56 [0.44, 5.53]	-
Abubaker 2007	70	143	77	153	14.3%	0.95 [0.60, 1.49]	+
Czarniecka 2015	39	127	32	106	9.1%	1.02 [0.59, 1.80]	+-
Durante 2007	14	56	12	36	4.1%	0.67 [0.27, 1.67]	
Elisei 2008	5	35	7	62	1.6%	1.31 [0.38, 4.48]	
Guan 2009	77	515	22	284	9.1%	2.09 [1.27, 3.44]	-
Howell 2011	44	86	13	133	1.9%	9.67 [4.75, 19.70]	_
Jo 2006	68	112	31	59	6.0%	1.40 [0.74, 2.64]	+
Kim 2005	33	64	8	15	2.4%	0.93 [0.30, 2.87]	
Kim 2006	107	149	31	54	4.8%	1.89 [0.99, 3.61]	
Lee 2006	32	58	14	42	2.7%	2.46 [1.08, 5.61]	
Liu 2005	26	47	26	54	4.1%	1.33 [0.61, 2.92]	
Liu 2014	49	80	22	52	3.9%	2.16 [1.06, 4.39]	
Nakayama 2007	20	26	5	14	0.6%	6.00 [1.44, 24.92]	· · · · ·
Namba 2003	14	38	24	88	3.4%	1.56 [0.69, 3.49]	
O'Neill 2010	8	60	7	41	2.7%	0.75 [0.25, 2.25]	
Park 2014	305	476	93	212	17.4%	2.28 [1.64, 3.17]	+
Riesco-Eizaguirre 2006	18	28	11	39	1.2%	4.58 [1.62, 12.98]	
Xing 2005	44	107	18	112	3.9%	3.65 [1.93, 6.88]	
Xing 2009	17	73	13	117	2.9%	2.43 [1.10, 5.36]	
Yip 2009	56	99	15	100	2.4%	7.38 [3.75, 14.53]	
Total (95% Cl)		2402		1790	100.0%	2.03 [1.76, 2.34]	•
Total events	1058		488				
Heterogeneity: Chi ² = 71.8	85, df = 20	(P < 0.0	0001); l²	= 72%			
Test for overall effect: Z =	9.68 (P <	0.00001)			-	U.UI U.I I 10 100
						F	avours experimental Pavours control

Figure 5. Random effect model of the odds ratios (ORs) with 95% confidence intervals (Cls) 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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	mutant	BRAF	wt BR	AF	Odds Ratio			Odds Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C		M-H, Fix	ed, 95% Cl	
Durante 2007	3	37	6	31	16.6%	0.37 [0.08, 1.61]		-	+	
Elisei 2008	3	37	3	63	5.6%	1.76 [0.34, 9.23]				
Fugazzola 2006	3	99	7	161	14.3%	0.69 [0.17, 2.72]			<u> </u>	
Henke 2015	8	340	7	168	25.3%	0.55 [0.20, 1.56]		-	t	
Ito 2009	1	242	3	389	6.3%	0.53 [0.06, 5.16]		-	<u> </u>	
Jo 2006	1	102	1	59	3.5%	0.57 [0.04, 9.35]	-			
Liu 2005	0	47	4	54	11.5%	0.12 [0.01, 2.25]	•		<u> </u>	
Nakayama 2007	3	26	0	14	1.5%	4.32 [0.21, 89.81]				
Namba 2003	7	38	5	88	6.8%	3.75 [1.11, 12.69]				
O'Neill 2010	3	60	2	41	6.2%	1.03 [0.16, 6.43]			<u> </u>	
Riesco-Eizaguirre 2006	1	28	1	39	2.2%	1.41 [0.08, 23.50]				
Total (95% CI)		1056		1107	100.0%	0.88 [0.55, 1.42]				
Total events	33		39							
Heterogeneity: Chi ² = 11.5	58, df = 10	(P = 0.3	1); ² = 14	%			0.01	0.1	1 10	100
Test for overall effect: Z =	0.51 (P =	0.61)				-	0.01	U.1	1 10 Fourier comt	100
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Figure 6. Fixed effect model of the odds ratios (ORs) with 95% confidence intervals (Cls) of the presence of distant metastasis associated with the BRAF V600E mutation is shown.

	mutant E	BRAF	wt BR	AF		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	M-H, Fixed, 95% Cl
Abubaker 2007	37	143	48	153	9.6%	0.76 [0.46, 1.27]	
Czarniecka 2015	34	127	26	106	5.8%	1.12 [0.62, 2.03]	
Durante 2007	15	43	7	32	1.5%	1.91 [0.67, 5.45]	
Elisei 2008	13	37	7	61	1.0%	4.18 [1.48, 11.79]	
Fugazzola 2004	7	18	9	29	1.2%	1.41 [0.41, 4.85]	
Fugazzola 2006	28	99	35	161	5.3%	1.42 [0.80, 2.53]	
Goutas 2007	2	15	9	40	1.2%	0.53 [0.10, 2.80]	
Guan 2009	151	515	45	284	11.4%	2.20 [1.52, 3.19]	-
He 2014	53	119	15	68	2.9%	2.84 [1.44, 5.59]	
Henke 2015	122	340	39	168	9.3%	1.85 [1.21, 2.82]	-
Howell 2011	40	86	22	133	2.6%	4.39 [2.35, 8.18]	· · ·
Ito 2009	48	242	87	389	14.9%	0.86 [0.58, 1.28]	+
Jo 2006	23	102	11	59	3.0%	1.27 [0.57, 2.84]	- -
Lee 2006	19	58	7	42	1.5%	2.44 [0.91, 6.49]	
Liu 2005	19	47	17	54	2.6%	1.48 [0.65, 3.35]	
Liu 2014	19	80	11	52	2.8%	1.16 [0.50, 2.69]	
Nakayama 2007	18	26	2	14	0.2%	13.50 [2.43, 74.87]	
Namba 2003	26	38	46	88	2.4%	1.98 [0.89, 4.41]	
O'Neill 2010	18	60	8	41	1.9%	1.77 [0.68, 4.57]	
Park 2014	349	476	111	212	11.4%	2.50 [1.78, 3.50]	+
Riesco-Eizaguirre 2006	23	28	16	39	0.7%	6.61 [2.08, 21.06]	
Sapio 2006	1	19	6	24	1.4%	0.17 [0.02, 1.53]	
Schulten 2015	4	14	1	11	0.2%	4.00 [0.38, 42.37]	
Xing 2005	31	107	16	112	3.1%	2.45 [1.25, 4.80]	
Xing 2009	15	73	13	117	2.2%	2.07 [0.92, 4.65]	
Total (95% CI)		2912		2489	100.0%	1.77 [1.56, 2.01]	•
Total events	1115		614				
Heterogeneity: Chi ² = 64.9	96, df = 24	(P < 0.0	001); l² =	63%			
Test for overall effect: Z =	8.80 (P <	0.00001)			F	avours experimental Favours control

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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	mutant E	mutant BRAF wt BRAF		AF		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H. Fixed, 95% CI
Elisei 2008	13	38	6	64	7.8%	5.03 [1.72, 14.73]	
Fugazzola 2004	5	18	5	29	7.3%	1.85 [0.45, 7.57]	
He 2014	45	119	14	68	29.3%	2.35 [1.17, 4.70]	
Howell 2011	11	86	3	133	5.4%	6.36 [1.72, 23.50]	
Kim 2006	32	149	4	54	12.2%	3.42 [1.15, 10.18]	
Xing 2005	23	107	9	112	18.2%	3.13 [1.38, 7.13]	 -
Xing 2009	19	53	9	76	12.5%	4.16 [1.70, 10.17]	— • —
Yip 2009	11	106	3	100	7.3%	3.74 [1.01, 13.84]	-
Total (95% CI)		676		636	100.0%	3.34 [2.36, 4.73]	•
Total events	159		53				
Heterogeneity: Chi ² = 3	3.44, df = 7	(P = 0.8	34); l ² = 09	%			
Test for overall effect: 2	Z = 6.77 (P	< 0.000	01)			Fa	vours experimental Favours control

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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