Systematic Review/Meta-analysis

BRAF mutation is associated with poor clinicopathological outcomes in colorectal cancer: A meta-analysis

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Abstract

Background/Aims: The clinical relevance of the *BRAF* mutation in colorectal carcinoma (CRC) remains controversial. We performed a comprehensive meta-analysis to evaluate the precise relationship of *BRAF* mutation to clinicopathological features.

Materials and Methods: A systematic search of the electronic databases, including PubMed, the Web of Knowledge, and the China Journal Net was performed between January 2005 and December 2015. Outcomes of interest included gender, tumor site, tumor differentiation, node involvement, tumor size, and AJCC stage. We calculated the pooled odds ratios (ORs) or risk ratios with 95% confidence intervals (CIs) for each study using a random or fixed-effect model.

Results: Twenty-five studies with a total of 13208 patients were included. *BRAF* mutation-positive CRC patients were 1464 (11.1%). Our meta-analysis revealed that, in patients with CRC, the *BRAF* mutation was associated with female, proximal site, poor differentiation, >5 cm size, and advanced AJCC stage.

Conclusions: This meta-analysis demonstrated that *BRAF* mutation was closely related to adverse pathological features and poor outcome of CRC.

Keywords: *BRAF* mutation, clinicopathological outcomes, colorectal cancer, meta-analysis

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INTRODUCTION

Colorectal carcinoma (CRC) is one of the most common malignancies and frequently takes a fatal course to human health worldwide.[1] The development of CRC is a multistep process which included chromosomal abnormalities, gene mutations, and epigenetic modifications.[2,3]

BRAF and *KRAS* are both members of the Ras/Raf/MEK/MAP kinase cascade, which transduces various growth signals from the cell surface to the nucleus. Mutations of the genes encoding the *KRAS* and *BRAF* have been implicated in colorectal carcinogenesis.[4] However, *KRAS* and *BRAF* mutations appear to be mutually exclusive.[5,6]

BRAF mutations occurred in 5–11% of CRC cases,[7] and *BRAF*-mutant CRC has been associated with clinicopathological features,[8,9] including sex, tumor location, differentiation, lymph node involvement, and clinical stage. Some previous reports indicated that CRCs with *BRAF* mutations tend to be at a lower clinical stage,[10,11] whereas other studies[12-14] revealed CRCs with altered *BRAF* apt to have a poor prognosis. Therefore,

Access this article online	
Quick Response Code:	Website: www.saudijgastro.com
	DOI: 10.4103/1319-3767.207712

How to cite this article: Li Y, Li W. *BRAF* mutation is associated with poor clinicopathological outcomes in colorectal cancer: A meta-analysis. Saudi J Gastroenterol 2017;23:144-9.

it is necessary to use *BRAF* to make standard clinical and pathological staging more accurately for more effective clinical management.[15] Thus, we conducted this meta-analysis to assess the correlation between the BRAF mutation and clinicopathological characteristics of the CRC.

MATERIALS AND METHODS

Search strategy

A comprehensive literature review was performed from January, 2005 to December, 2015, using PubMed, Web of Knowledge, and the China Journal net. The search terms used were "BRAF," "colon," "rectal," "rectum," "tumor," "cancer," "neoplasm," and "malignant." The reference lists of relevant studies were checked manually to locate any missing studies.

Inclusion and exclusion criteria

Criteria for eligibility of a study included in this meta-analysis were (1) Detection of the *BRAF* mutation in the CRC tissues; (2) the studies published in English and Chinese; (3) when several studies were reported from the same authors or organizations, the meta-analysis enrolling the most recent or highest quality study only if the most recent one did not fit the inclusion criteria. Studies were excluded if (1) Studies were case reports, letters, and reviews without original data; animal or laboratory studies; (2) studies without clinicopathologic data were excluded; (3) repeated studies based on the same database or patients.

Data extraction

Two review authors (L.Y. and L.W.) independently selected studies for inclusion and extracted the data. A third researcher (Z.X.) arbitrated in the event of any disagreement. The decision for inclusion in the analysis was made by consensus. Full-text copies of potentially relevant studies were obtained. The following variables were recorded: authors, sex, number of patients, age of patients, histological cancer type, clinicopathological characteristics, and *BRAF* mutation rate.

Statistical analysis

A formal meta-analysis was done for all studies. The statistical analysis was carried out using the Review Manager 5.0. 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. For the pooled analysis of the correlation between *BRAF* mutation and clinicopathological features (sex, tumor location, differentiation, lymph node involvement, and clinical stage), odds ratios (ORs), and 95% CI were combined to estimate the effect.

RESULTS

Study selection

We identified 2292 potentially relevant articles [Figure 1]. After exclusion of duplicate references, nonrelevant literature, and those manuscripts that did not satisfy the inclusion criteria, 76 articles were considered for the meta-analysis. After careful review of the full texts of these articles, 25 studies were included. The study characteristics are summarized in Table 1.

After this review, 25 studies met the inclusion/exclusion criteria. A meta-analysis was performed of the 25 studies that evaluated 13208 patients. *BRAF* mutation-positive CRC patients were 1464, giving an overall frequency of 11.1%. The patient demographics for the 25 studies are presented in Table 1. All papers were retrospective chart reviews. The publication dates ranged from 2005 to 2015. The study sizes ranged from 43 to 2166 patients.

Twenty-four studies including 13043 patients demonstrated that there was a significant association between BRAF mutation and female gender (OR = 1.87; 95% CI = 1.66–2.09) [Figure 2]. Except this above mentioned parameter, controversies also existed on the correlation among tumor location, differentiation, lymph node metastasis, tumor size, AJCC stage, and *BRAF* mutation in these included studies. Eleven studies including 5307 patients were analyzed for the association between *BRAF* mutation and the location of the colorectal tumor. There was a significant association between *BRAFV600E* mutation and proximal colon tumor

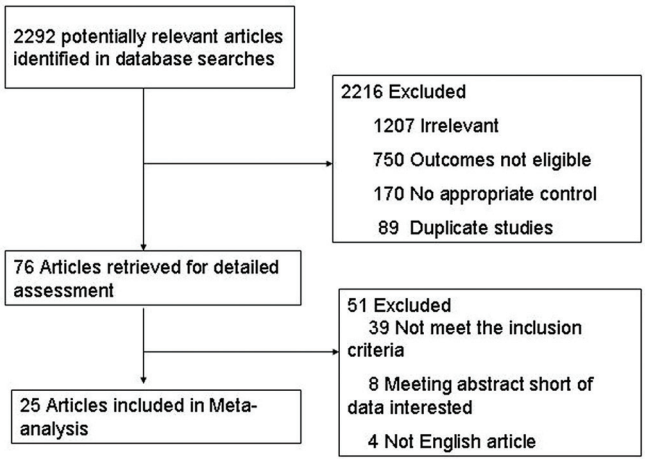

Figure 1: Flowchart of the results of the literature search

Table 1: Overview of the reviewed studies

Author, Year	Country	No. of patients	Sex (male/female)	Patient source	Mean age, years	*BRAF* mutation rate (%)
Ang *et al*. 2009[16]	Australia	735	440/295	University of Western Australia	-	7
Bagadi *et al*. 2012[17]	India	100	74/26	-	56	17
Bozzao *et al*. 2012[18]	Italy	200	119/90	Medical Genetics Unit	61.44	6.2
English *et al*. 2008[19]	Australia	582	291/291	Melbourne	-	-
Fariña-Sarasqueta *et al*. 2010[20]	Netherlands	364	198/166	PAMM Laboratory	-	-
Gao *et al*. 2012[21]	China	915	538/377	Peking University Cancer Hospital	60	7.4
Ikehara *et al*. 2005[22]	Japan	116	74/42	Kobe University Hospital	62.1	
Kadiyska *et al*. 2007[11]	Bulgaria	140	64/76	Queen Giovanna Hospital	59	5.7
Lee *et al*. 2008[23]	South Korea	134	69/47	Seoul National University Hospital	-	4.5
Li *et al*. 2006[24]	Australia	275	132/100	Royal Adelaide Hospital	68.4	8
Martinetti *et al*. 2014[25]	Italy	159	90/69	Tirana University Hospital	61.7	6.3
Phipps *et al*. 2012[26]	USA	1980	900/1080	Western Washington State	-	12
Rako *et al*. 2012[5]	Croatia	75	46/29	University Hospital Center Zagreb	60.24	8.5
Roth *et al*. 2010[27]	Switzerland	1404	755/552	Geneva University	-	7.9
Samowitz *et al*. 2005[28]	USA	911	473/413	University of Utah Health Sciences Center	-	9.5
Shaukat *et al*. 2010[29]	USA	165	-	University of Minnesota	-	-
Tie *et al*. 2010[30]	Australia	525	261/264	Royal Melbourne Hospital, Western Hospital	70.5	9.9
Yaeger *et al*. 2014[6]	USA	515	268/247	Memorial Sloan-Kettering Cancer Center	-	5
Ye *et al*. 2015[31]	China	535	306/229	Peking University Third Hospital	65	4.4
Yokota *et al*. 2011[32]	Japan	229	134/95	Aichi Cancer Center Hospital	-	6.6
Yoshitake *et al*. 2007[33]	Japan	43	30/13	Dokkyo University School of Medicine	64.2	9.3
Zlobec *et al*. 2010[9]	Switzerland	374	171/200	University Hospital of Basel	-	-

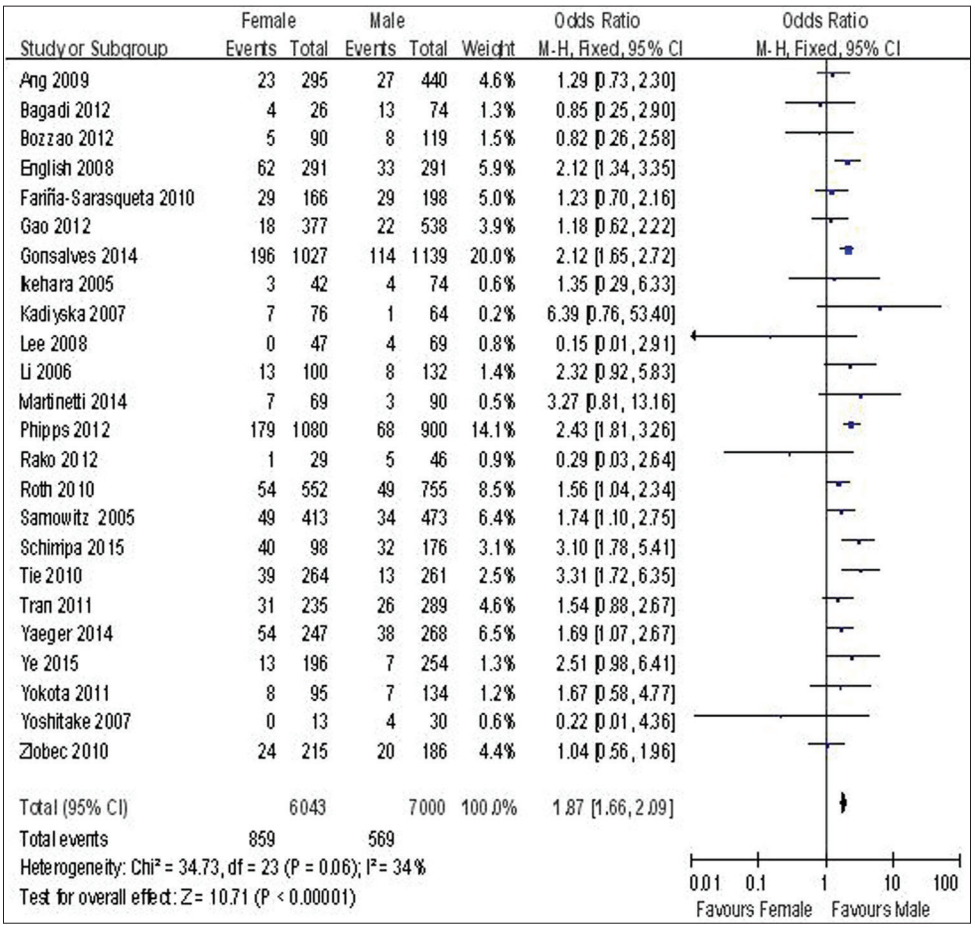

Figure 2: The association of *BRAF* mutation with demographics. Fixed effects model of the odds ratios (ORs) with 95% confidence intervals (CIs) for the association of *BRAF* mutation with gender

location (OR = 5.87; 95% CI = 3.72–9.24) [Figure 3a]. Twelve studies including 3569 patients were analyzed for the association between BRAF mutation and colorectal differentiation. There was a significant association between *BRAF* mutation and poor differentiation (OR = 3.57; 95% CI = 2.82–4.53) [Figure 3b]. In addition, two studies including 399 patients and 9 studies including 4154 patients reported the association between *BRAF* mutation and tumor size or AJCC stage. There was a significant correlation between the *BRAF* mutation and tumor size (OR = 2.63; 95% CI = 1.08–6.39) [Figure 3d], advanced AJCC stage [OR = 1.63; 95% CI = 1.26–2.13) [Figure 3e]. However, for the cases of lymph node metastasis, 4 studies including 1142 patients were analyzed. The meta-analysis suggested that *BRAF* mutation was not correlated with lymph node metastasis (OR = 0.74; 95% CI = 0.47–1.17) [Figure 3c].

DISCUSSION

In our study, we confirmed that BRAF mutation was significantly associated with the high-risk clinicopathological factors of CRC and poor clinical outcome. To evaluate the relationship between *BRAF* mutation status and adverse clinicopathological outcomes, we performed a meta-analysis of 25 studies that evaluated 13208 patients. In our study, CRC patients with *BRAF* mutation exhibited 5.8 fold increase in female gender, poor differentiation, higher AJCC stages, proximal site, and size >5 cm comapared with patients with the wild-type form of the *BRAF* gene.

The *BRAF* V600E mutation has been validated independently as prognostic for overall survival and variable results have been obtained related to this mutation's association with traditional risk factors for higher mortality rate of CRC patients.[6,26] Recently, significant correlations were found between *BRAF* mutation and the presence of right-sided tumors, poor differentiation, and mucinous histology.[9,24,29,32,34,35] Our meta-analysis provides new insights into the clinicopathological importance of the *BRAF* mutation in CRC and includes studies published after 2005.

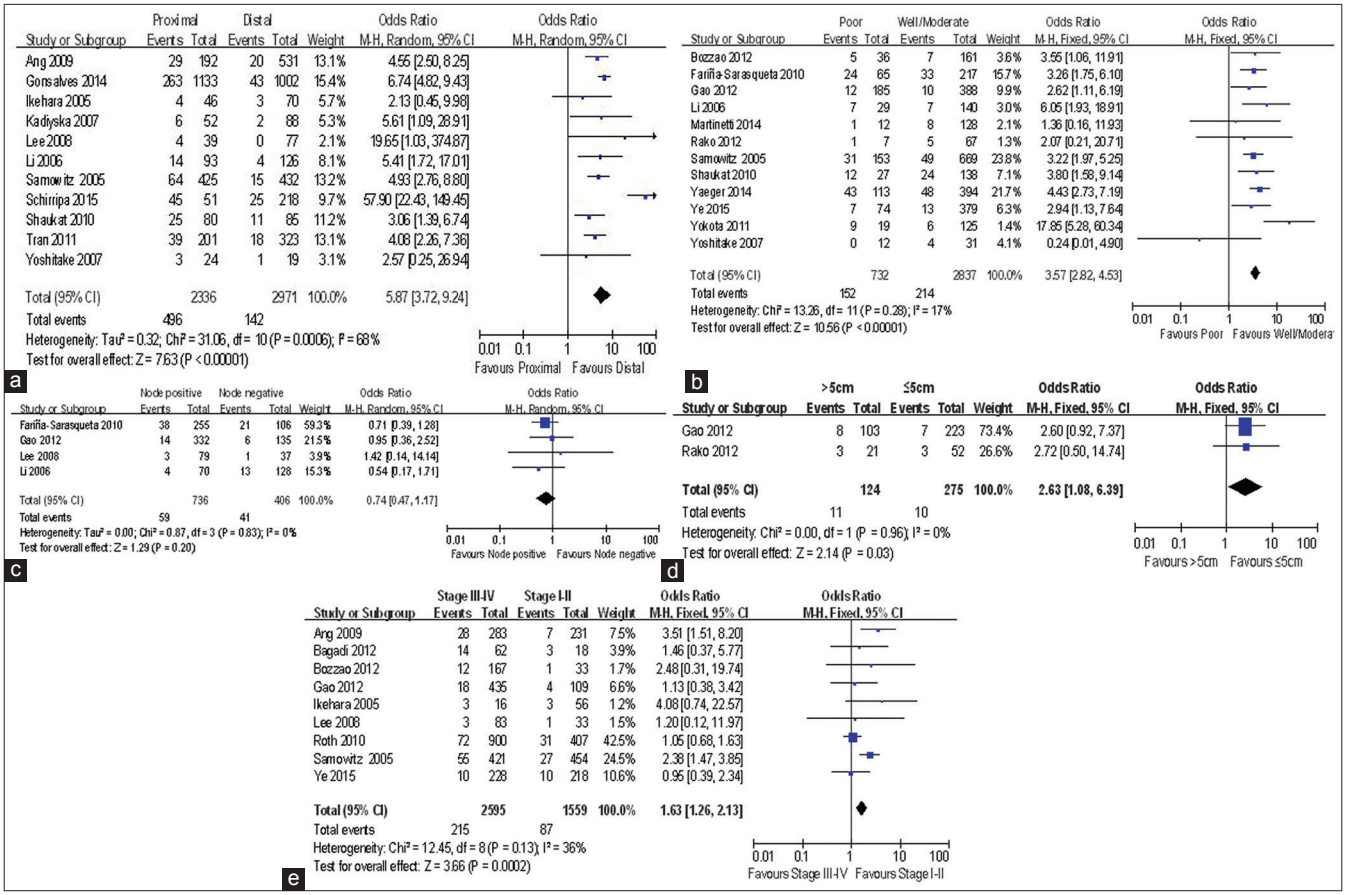

Figure 3: Random effects model of the odds ratios (ORs) with 95% confidence intervals (CIs) of the association of *BRAF* mutation with tumor site; (b) fixed effects model of the odds ratios (ORs) with 95% confidence intervals (CIs) of the association of *BRAF* mutation with tumor differentiation; (c) fixed effects model of the odds ratios (ORs) with 95% confidence intervals (CIs) of the association of *BRAF* mutation with node involvement; (d) fixed effects model of the odds ratios (ORs) with 95% confidence intervals (CIs) of the association of *BRAF* mutation with tumor size; (e) fixed effects model of the odds ratios (ORs) with 95% confidence intervals (CIs) of the association of *BRAF* mutation with AJCC stage

Cantwell-Dorris reported the *BRAF* mutation of CRC with lymphatic metastasis as 5 to 10 times higher than that of CRC with lymph node negative.[36] Compared to our study, the *BRAF* mutation did not show statistically significant association with lymph node metastasis. This might be explained by the limited studies included in our research.

Several mechanisms are involved in the aggressive phenotype of CRC that is promoted by the *BRAF* mutation. Ikenoue *et al*.[37] indicated that the *BRAF* mutations of CRC can promote the activation of ERK, which activates downstream transcription factors to induce a range of biochemical processes including cell differentiation, proliferation, growth, while acting as the inhibitor of apoptosis.[38] *BRAF* mutation of CRC also display deficiency in mismatch repair (MMR). The prevalence of *BRAF* mutation in MMR-deficient tumors has been shown to be three-fold greater than in MMR-proficient tumors.[39]

There are several limitations of our meta-analysis. First, we did not evaluate the methods used to detect *BRAF* mutations for lacking data, which may affect the results. Second, we did not collect data on the treatment and clinical outcomes to analyze effect of the *BRAF* mutation on the overall clinical outcome. In addition, selection bias is also the domain that could lead to a biased estimate of the procedural effects in this analysis.

CONCLUSIONS

This meta-analysis demonstrated that *BRAF* mutation was closely related to adverse pathological features and poor outcome of CRC. *BRAF* mutation should be considered as a poor prognostic marker in CRC, and *BRAF* mutational analysis could result in better management for individual CRC patients.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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