**INTRODUCTION**

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

*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. However, *KRAS* and *BRAF* mutations appear to be mutually exclusive.

*BRAF* mutations occurred in 5–11% of CRC cases and *BRAF*-mutant CRC has been associated with clinicopathological features, 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 whereas other studies revealed CRCs with altered *BRAF* apt to have a poor prognosis. Therefore,
Li and Li: BRAF mutation in colorectal cancer

it is necessary to use BRAF to make standard clinical and pathological staging more accurately for more effective clinical management.\cite{19} 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 $\chi^2$ 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](image-url)
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 |
| Bozzi 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 | - | - |
| Farfà-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 [23] | Bulgaria | 140 | 64/76 | Queen Giovanna Hospital | 59 | 5.7 |
| Lee et al. 2008 [24] | South Korea | 134 | 69/47 | Seoul National University Hospital | - | 4.5 |
| Li et al. 2006 [25] | Australia | 275 | 132/100 | Royal Adelaide Hospital | 68.4 | 8 |
| Martinetti et al. 2014 [26] | Italy | 159 | 90/69 | Tirana University Hospital | 61.7 | 6.3 |
| Phipps et al. 2012 [27] | USA | 1980 | 900/1080 | Western Washington State | - | 12 |
| Rako et al. 2012 [28] | Croatia | 75 | 46/29 | University Hospital Center Zagreb | 60.24 | 8.5 |
| Roth et al. 2010 [29] | Switzerland | 1404 | 755/552 | Geneva University | - | 7.9 |
| Samowitz et al. 2005 [30] | USA | 911 | 473/431 | University of Utah Health Sciences Center | - | 9.5 |
| Shaukat et al. 2010 [31] | USA | 165 | - | University of Minnesota | - | - |
| Tie et al. 2010 [32] | Australia | 525 | 261/264 | Royal Melbourne Hospital, Western Hospital | 70.5 | 9.9 |
| Yaeger et al. 2014 [33] | USA | 515 | 268/247 | Memorial Sloan-Kettering Cancer Center | - | 5 |
| Ye et al. 2015 [34] | China | 535 | 306/229 | Peking University Third Hospital | 65 | 4.4 |
| Yokota et al. 2011 [35] | Japan | 229 | 134/95 | Aichi Cancer Center Hospital | - | 6.6 |
| Yoshitake et al. 2007 [36] | Japan | 43 | 30/13 | Dokkyo University School of Medicine | 64.2 | 9.3 |
| Zlobec et al. 2010 [37] | 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.
Li and Li: BRAF mutation in colorectal cancer

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 compared 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.[6,28] 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.
Cantwell-Dorris reported the \textit{BRAF} mutation of CRC with lymphatic metastasis as 5 to 10 times higher than that of CRC with lymph node negative. Compared to our study, the \textit{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 \textit{BRAF} mutation. Ikenoue et al.\cite{13} indicated that the \textit{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.\cite{13} \textit{BRAF} mutation of CRC also display deficiency in mismatch repair (MMR). The prevalence of \textit{BRAF} mutation in MMR-deficient tumors has been shown to be three-fold greater than in MMR-proficient tumors.\cite{13}

There are several limitations of our meta-analysis. First, we did not evaluate the methods used to detect \textit{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 \textit{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 \textit{BRAF} mutation was closely related to adverse pathological features and poor outcome of CRC. \textit{BRAF} mutation should be considered as a poor prognostic marker in CRC, and \textit{BRAF} mutational analysis could result in better management for individual CRC patients.

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Conflicts of interest
There are no conflicts of interest.

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