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Tracking the Correlation Between CpG Island Methylator Phenotype and Other Molecular Features and Clinicopathological Features in Human Colorectal Cancers: A Systematic Review and Meta-Analysis

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OBJECTIVES: The controversy of CpG island methylator phenotype (CIMP) in colorectal cancers (CRCs) persists, despite many studies that have been conducted on its correlation with molecular and clinicopathological features. To drive a more precise estimate of the strength of this postulated relationship, a meta-analysis was performed.

METHODS: A comprehensive search for studies reporting molecular and clinicopathological features of CRCs stratified by CIMP was performed within the PubMed, EMBASE, and Cochrane Library. CIMP was defined by either one of the three panels of gene-specific CIMP markers (Weisenberger panel, classic panel, or a mixture panel of the previous two) or the genome-wide DNA methylation profile. The associations of CIMP with outcome parameters were estimated using odds ratio (OR) or weighted mean difference (WMD) or hazard ratios (HRs) with 95% confidence interval (CI) for each study using a fixed effects or random effects model.

RESULTS: A total of 29 studies involving 9,393 CRC patients were included for analysis. We observed more *BRAF* mutations (OR 34.87; 95% CI, 22.49–54.06) and microsatellite instability (MSI) (OR 12.85 95% CI, 8.84–18.68) in CIMP-positive vs. -negative CRCs, whereas *KRAS* mutations were less frequent (OR 0.47; 95% CI, 0.30–0.75). Subgroup analysis showed that only the genome-wide methylation profile-defined CIMP subset encompassed all *BRAF*-mutated CRCs. As expected, CIMP-positive CRCs displayed significant associations with female (OR 0.64; 95% CI, 0.56–0.72), older age at diagnosis (WMD 2.77; 95% CI, 1.15–4.38), proximal location (OR 6.91; 95% CI, 5.17–9.23), mucinous histology (OR 3.81; 95% CI, 2.93–4.95), and poor differentiation (OR 4.22; 95% CI, 2.52–7.08). Although CIMP did not show a correlation with tumor stage (OR 1.10; 95% CI, 0.82–1.46), it was associated with shorter overall survival (HR 1.73; 95% CI, 1.27–2.37).

CONCLUSIONS: The meta-analysis highlights that CIMP-positive CRCs take their own molecular feature, especially overlapping with *BRAF* mutations, and clinicopathological features and worse prognosis from CIMP-negative CRCs, suggesting CIMP could be used as an independent prognostic marker for CRCs.

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INTRODUCTION

Aberrant DNA methylation is a hallmark of human cancer and can be summarized as global hypomethylation and regional hypermethylation. Regional hypermethylation refers to the aberrant methylation of normally unmethylated sequences, most of which are clusters of CpG sites, denoted CpG island. Specifically, regional hypermethylation of promoter-associated CpG islands of tumor-suppressor and repair genes is involved in the initiation and progression of cancer by transcription silencing.[1,2]

A subgroup of human cancers is known to have frequent aberrant DNA methylation of the CpG island, referred to as the CpG island methylator phenotype (CIMP). CIMP was first identified in colorectal cancers (CRCs).[3] For the determination of CIMP in CRCs, three panels of CIMP marker genes were available: a classic five-marker panel (*MINT1*, *MINT2*, *MINT31*, *CDKN2A* (p16), and *hMLH1*),[3,4] the Weisenberger five-marker panel (*CACNA1G*, *IGF2*, *NEUROG1*, *RUNX3*, and *SOCS1*),[5] and a mixture panel of both. Both classic and Weisenberger CIMP-positive CRCs have been reported to be

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associated with proximal tumor location, microsatellite instability (MSI), and *BRAF* mutations.[5,6] Whereas the classic panel outperformed in predicting clinical outcomes, the Weisenberger panel was superior in detecting known clinicopathological features of CIMP but was inferior in prognostication power.[7] Recently, genome-wide DNA methylation analysis was performed using the Infinium bead array to identify the CIMP subtype in human cancers, including CRCs. CRCs now can be categorized into CIMP-positive and -negative subtypes or CIMP-high, -low, and -negative subtypes.

It has been found that CIMP-positive or CIMP-high CRCs have a close association with molecular and clinicopathological features.[8–10] Identifying the correlation of CIMP with molecular aberrations such as mutation of *BRAF* in CRCs may improve our understanding of carcinogenesis, identify strategies for subdividing patients into relevant subgroups, and highlight novel molecular target agents. Although the molecular mechanisms of CRC carcinogenesis remain unclear, both genetic and epigenetic alterations are considered to be important. Genetic alterations are responsible for the activation of oncogenes and the inactivation of tumor-suppressor genes, whereas epigenetic alterations through DNA methylation are known to play an important role in inhibiting the expression of tumor-related genes.

The presence of CIMP in CRCs has been reported to be associated with worse prognosis,[8,9] but controversial data regarding the correlation of CIMP with molecular and clinicopathological features makes it difficult to understand the internal mechanism. This is possibly because of limited sample size or confounding variables. Therefore, we initiated an international collaborative effort to evaluate the molecular features such as *BRAF*, *KRAS* mutations, MSI, and clinicopathological features and prognosis between CIMP-positive and -negative CRCs.

METHODS

Search strategy. Standard guidelines for conducting and reporting a systematic review and meta-analysis were followed.[11] All data available before 1 June 2015 from three electronic databases (PubMed, EMBASE, and Cochrane Library) were searched using a combination of MESH terms: colorectal cancer OR colorectal carcinoma PLUS CpG island methylator phenotype OR CIMP. All eligible studies were retrieved, and their bibliographies were hand-searched to capture for other relevant publications. Two reviewers (L.Z. and M.A.) independently screened all abstracts, following exclusion criteria for the first-round selection. Of the remaining articles, both reviewers independently evaluated the full text, following inclusion criteria for the second-round selection. Discrepancies between the two reviewers were resolved via discussion with three senior authors (J.J., W.-G.Z., and D.Y.).

Exclusion criteria. Abstracts, letters, editorials and expert opinions, reviews without original data, case reports, and studies that were not written in English were excluded. Studies or data were also excluded if: (i) they reported on non-colorectal or non-human tissues or colorectal polyps or hereditary forms of CRC; (ii) selection bias of study design existed, e.g., advanced CRCs, MSI-positive CRCs, CIMP-positive colon cancer or rectal cancer, and so on; (iii) relevant molecular or clinicopathological outcome parameters were not clearly reported; (iv) it was impossible to extract the appropriate data from the published results; and (v) there was overlap between authors or centers in the published literature and only the most recent or complete study was used.

Inclusion criteria. The inclusion criteria were as follows: (i) CIMP status was defined by gene-specific methylation analysis with restriction to two respective gene panels of markers (classic five-marker panel and Weisenberger five-marker panel) or a mixing of the two gene panels; (ii) CIMP status was defined by genome-wide methylation analysis; (iii) the studies evaluated the relationship between CIMP and *BRAF*, *KRAS*, MSI, or clinicopathological parameters such as gender, age, tumor location, histology, differentiation, tumor stage, or overall survival; (iv) sufficient published data could be used to estimate an odds ratio (OR) or weighted mean difference (WMD) or hazard ratio (HR) with 95% confidence interval (CI).

Quality assessment. Jadad Scale and MINORS are usually used to assess the quality of randomized controlled trials and nonrandomized controlled trials, respectively.[12,13] However, they are insufficiently validated for molecular studies. Instead, we made strict criteria for included studies such as no exclusion in specimen for a single-aim study of colon cancer or rectal cancer, all stage of tumors, and no exclusion based on molecular marker. Moreover, we made a subgroup analysis to examine whether the definition or the method used for CIMP (e.g., Weisenberger panel, classic panel, mixture panel, and genome-wide DNA methylation profile) influenced the results.

Data extraction. The following data were collected from each study: first author's surname, publication date, study method, sample size, total number of patients with positive CIMP and negative CIMP, and number of patients divided by *BRAF*, *KRAS*, MSI, age, gender, tumor location, histology, differentiation status, tumor TNM stage, and overall survival in those with and without CIMP, respectively. We did not define a minimum number of patients for inclusion in our meta-analysis.

Statistical analysis. ORs with 95% CIs were used for comparisons of binary measurements (e.g., *BRAF*, *KRAS*, MSI, gender, tumor location, histology, differentiation, and tumor stage), and WMD approach was analyzed for effects on quantitative measurements (e.g., age) according to the Woolf method. A weighted average of the individual adjusted log HRs was used to summarize the association between CIMP and overall survival, with the weights inversely proportional to the variance of the log HR of each study. Heterogeneity assumption was confirmed by the χ^2-based Q-test. A P value of >0.10 for the Q-test indicated a lack of heterogeneity among the studies, and therefore the OR or

WMD or HR estimate for each study was calculated by the fixed effects model. Otherwise, the random effects model was used. The significance of the pooled OR or WMD or HR was determined by the *Z*-test and $P<0.05$ was considered statistically significant. Sensitivity analyses were carried out to determine whether modification of the inclusion criteria for this meta-analysis affected the final results. An estimate of potential publication bias was carried out using the funnel plot. An asymmetric plot suggested possible publication bias. Funnel plot asymmetry was assessed using Egger's linear regression test, a linear regression approach to measure funnel plot asymmetry on the natural logarithm scale of the OR, WMD, or HR. The significance of the intercept was determined by the *t*-test, as suggested by Egger ($P<0.05$ was considered representative of statistically significant publication bias). All statistical tests were performed with Review Manager Version 5.0 (The Cochrane Collaboration, Oxford, UK).

RESULTS

Study eligibility. Initially, 409 articles were identified for further selection from 3 databases (Figure 1). Articles were excluded after title screening or abstract screening or full-text evaluation by the reviewers. By checking the relevant bibliography, one additional article was included.

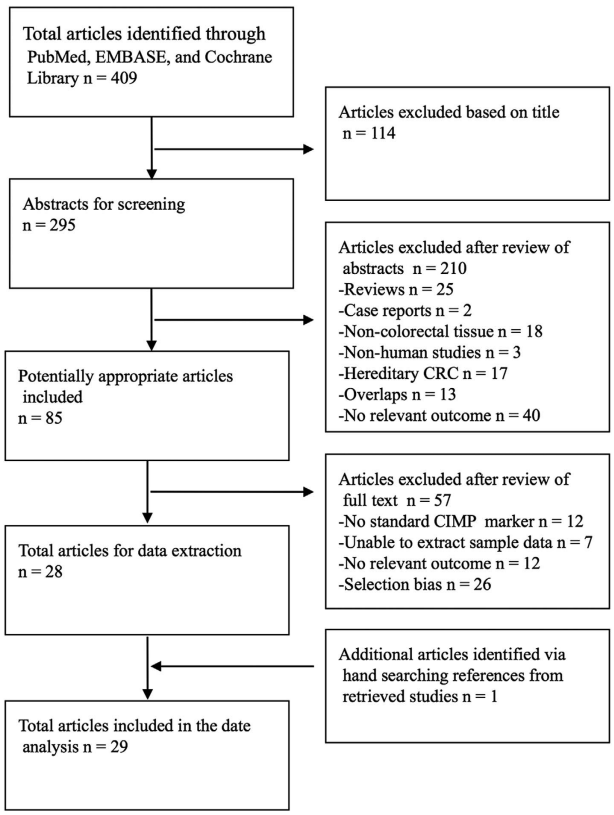

Figure 1 Flowchart of literature selection. CIMP, CpG island methylator phenotype; CRC, colorectal cancer.

Study characteristics. A total of 29 publications including 9,393 patients met the basic inclusion criteria,[5,7,8,14–39] of which 25 investigated for *BRAF* mutations, 18 for *KRAS* mutations, 20 for MSI, 24 for gender, 13 for age, 22 for tumor location, 7 for histology, 9 for differentiation, 14 for tumor stage, and 5 for overall survival. Among these studies, sample sizes ranged from 84 to 903 (Supplementary Table S1 online). In all, 7 studies used samples from Asia,[7,19,25,27,29,35,36] 5 from Australia,[5,14,20,22,36] 12 from Europe,[8,15,17,18,21,23,30–34,39] and 3 from the United States.[16,26,28] In addition, two studies used mixed samples from Hong Kong and United States,[24] and the Netherland and Canada,[38] respectively. Figure 2 lists the risk of bias of each included study from selection, exposure assessment, other variable assessment, outcome assessment, and confounding factors. Based on a strict exclusion and inclusion criteria, the studies with high risk in selection bias were not included. Although six studies in other variable assessment were rated as high risk, they clearly stated the methods for the assessment of CIMP, *BRAF* mutations, *KRAS* mutations, and MSI.

Molecular features

BRAF mutations. In all, 25 studies investigated the *BRAF* mutations in CRCs, examining a total of 7,627 CRCs: 10 studies for Weisenberger panel, 2 studies for classic panel, 9 studies for mixture panel, and 4 studies for genome-wide DNA methylation profile.

The overall OR for *BRAF* mutations in CIMP-positive vs. -negative CRCs was 34.87 (95% CI, 22.49–54.06; $P<0.00001$; Figure 3). Subgroup analyses of Weisenberger panel, classic panel, mixture panel, and genome-wide DNA methylation profile showed consistent results. Notably, we found that only the genome-wide methylation profile-defined CIMP subset of CRCs encompassed all *BRAF*-mutated CRCs.

KRAS mutations. In all, 18 studies investigated the *KRAS* mutations in CRCs, examining a total of 5,209 CRCs: 7 studies for Weisenberger panel, 3 studies for classic panel, 4 studies for mixture panel, and 4 studies for genome-wide DNA methylation profile. The overall OR for *KRAS* mutations in CIMP-positive vs. -negative CRCs was 0.47 (95% CI, 0.30–0.75; $P=0.001$; Figure 4). Subgroup analyses with Weisenberger panel and mixture panel showed that *KRAS* mutations frequently occurred in CIMP-negative CRCs, whereas classic panel and genome-wide DNA methylation profile did not show any differences in comparison of CIMP-positive and -negative CRCs.

Microsatellite instability. In all, 20 studies investigated the MSI status of CRCs, examining a total of 6,827 CRCs: 9 studies for Weisenberger panel, 1 study for classic panel, 7 studies for mixture panel, and 3 studies for genome-wide DNA methylation profile. A strong correlation between MSI and CIMP was achieved by OR 12.85 (95% CI, 8.84–18.68; $P<0.00001$; Figure 5). All of the subgroup analyses showed a similar trend, although all with large heterogeneity.

Clinicopathological features

Gender. In all, 24 studies investigated the correlation between CIMP and gender in CRCs, examining a total of

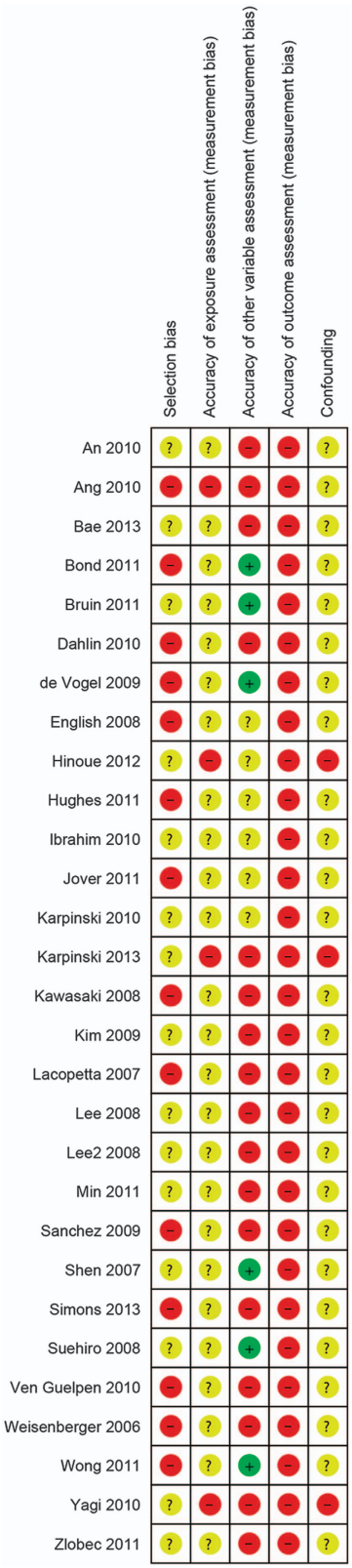

Figure 2 Risk of bias of each included study. Green cycle: study with high risk of bias; red cycle: study with low risk of bias; yellow cycle: study with insufficient information for assessing risk of bias.

7,298 CRCs: 9 studies for Weisenberger panel, 3 studies for classic panel, 8 studies for mixture panel, and 4 studies for genome-wide DNA methylation profile. The overall OR for the proportions of males in CIMP-positive vs. -negative CRCs was 0.64 (95% CI, 0.56–0.72; $P<0.00001$; Supplementary Figure S1 online). All of the subgroup analyses showed that more females took a leading position in CIMP-positive CRCs except for the subgroup of the classic panel.

Age. A total of 3,840 CRC patients either CIMP positive or CIMP negative in 13 studies were analyzed at the age at disease diagnosis: 8 studies for Weisenberger panel, 3 studies for mixture panel, and 2 studies for genome-wide DNA methylation profile. Because of lack of data from the classic panel, only three subgroup analyses were performed. The overall WMD for the age at disease diagnosis in CIMP-positive vs. -negative CRCs was 2.77 (95% CI, 1.15–4.38; $P=0.0008$; Supplementary Figure S2 online). Subgroup analyses of the Weisenberger panel and the genome-wide DNA methylation profile both showed that the CIMP phenomenon was much common in elder CRCs, whereas the mixture panel showed no differences.

Tumor location. In all, 22 studies investigated the correlation between CIMP and tumor locations in CRCs, examining a total of 6,740 CRCs: 9 studies for Weisenberger panel, 3 studies for classic panel, 6 studies for mixture panel, and 4 studies for genome-wide DNA methylation profile. The overall OR for the proportions of proximal location in CIMP-positive vs. -negative CRCs was 6.91 (95% CI, 5.17–9.23; $P<0.00001$; Supplementary Figure S3 online). All of the subgroup analyses strongly supported that CIMP-positive CRCs more commonly occurred in the proximal location.

Histology. In all, 7 studies investigated the correlation between CIMP and histological origin in CRCs, examining a total of 2,537 CRCs: 2 studies for Weisenberger panel, 4 studies for mixture panel, and 1 study for genome-wide DNA methylation profile. The overall OR for the proportions of mucinous type in CIMP-positive vs. -negative CRCs was 3.81 (95% CI, 2.93–4.95; $P<0.00001$; Supplementary Figure S4 online). Consistent results among the subgroup analyses strongly supported that CIMP-positive CRCs are associated with mucinous origin.

Differentiation. Nine studies investigated the correlation between CIMP and differentiation status in CRC cells, examining a total of 3629 CRCs: three studies for Weisenberger panel, one study for classic panel, four studies for mixture panel, and one study for genome-wide DNA methylation profile. The overall OR for the proportions of poor differentiation in CIMP positive vs. negative CRCs was 4.22 (95% CI, 2.52–7.08; $P<0.00001$; Supplementary Figure S5 online). All of the subgroup analyses strongly supported that CIMP-positive CRCs are associated with poor differentiation.

Tumor stage. In all, 14 studies investigated the correlation between CIMP and tumor stage in CRCs, examining a total of 3,882 CRCs: 4 studies for Weisenberger panel, 2 studies for classic panel, 5 studies for mixture panel, and 3 studies for genome-wide DNA methylation profile. The overall OR for the proportions of stages III and IV in CIMP-positive vs. -negative CRCs was 1.10 (95% CI, 0.82–1.46; $P=0.53$; Supplementary Figure S6 online). In the subgroup analyses,

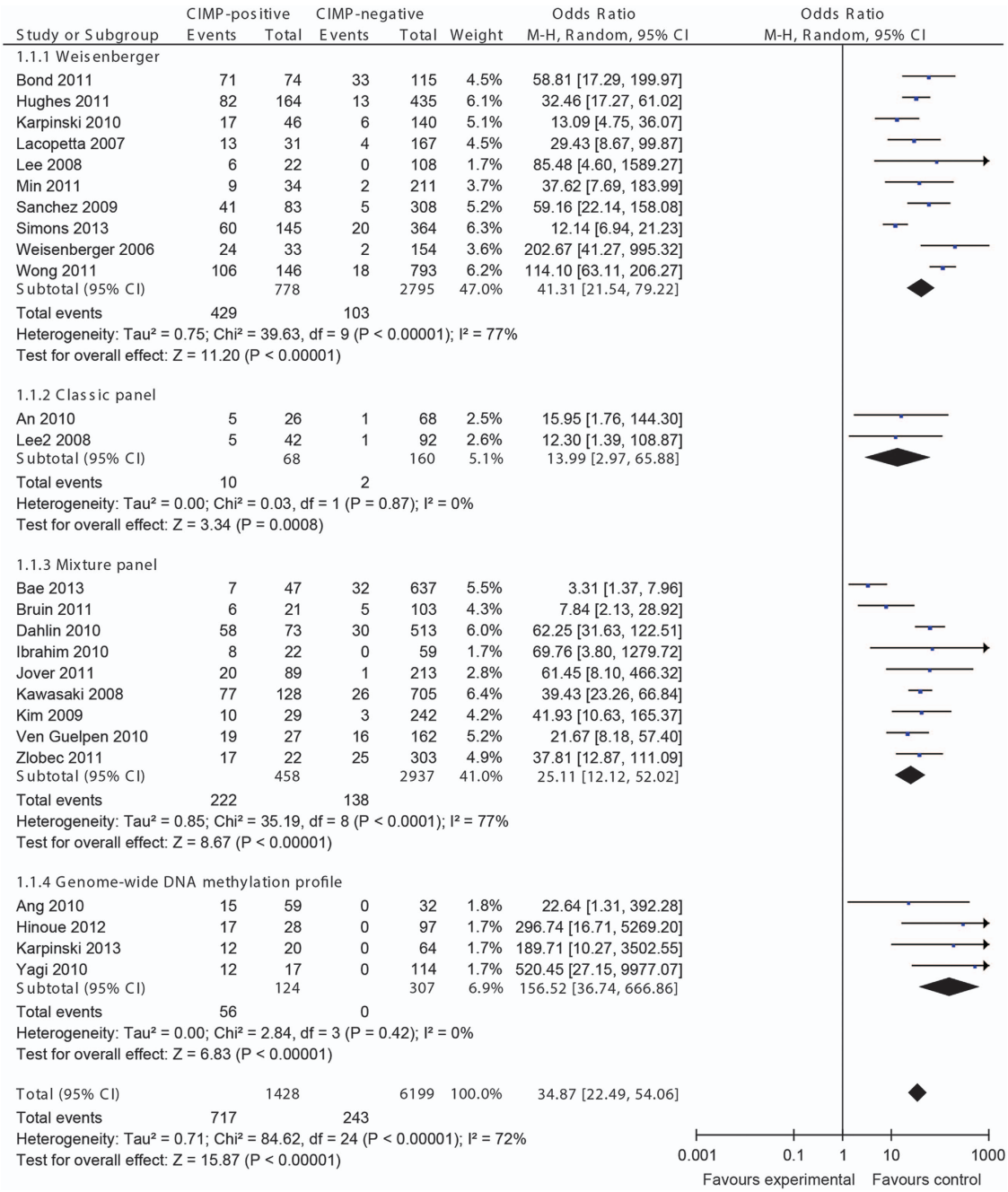

Figure 3 Meta-analysis investigating the frequency of *BRAF* mutations in CpG island methylator phenotype (CIMP)-positive vs. -negative colorectal cancers (CRCs). Random effect meta-analysis showed more *BRAF* mutations in CIMP-positive CRCs. CI, confidence interval.

CIMP-positive CRCs clearly did not associate with advanced tumor stages.

Overall survival. In total, four studies compared the overall survival of CIMP-positive and -negative CRCs: two studies for Weisenberger panel and two studies for mixture panel. Because of the insufficient data, we could only make a pooled analysis instead of a subgroup analysis. CIMP-positive CRCs were significantly associated with shorter overall survival (HR 1.73; 95% CI, 1.27–2.37; $P = 0.0005$; Figure 6a). A funnel plot clearly showed that no heterogeneity existed among these four included studies (Figure 6b).

Publication bias. Begg's funnel plot was performed to assess publication bias. The heterogeneity tests for comparing the 29 combined studies showed heterogeneity in some analyses such as *BRAF*, *KRAS*, MSI, age, tumor location, differentiation, and tumor stage. However, no single study influenced the pooled OR or WMD qualitatively as indicated by the sensitivity analyses (data not shown).

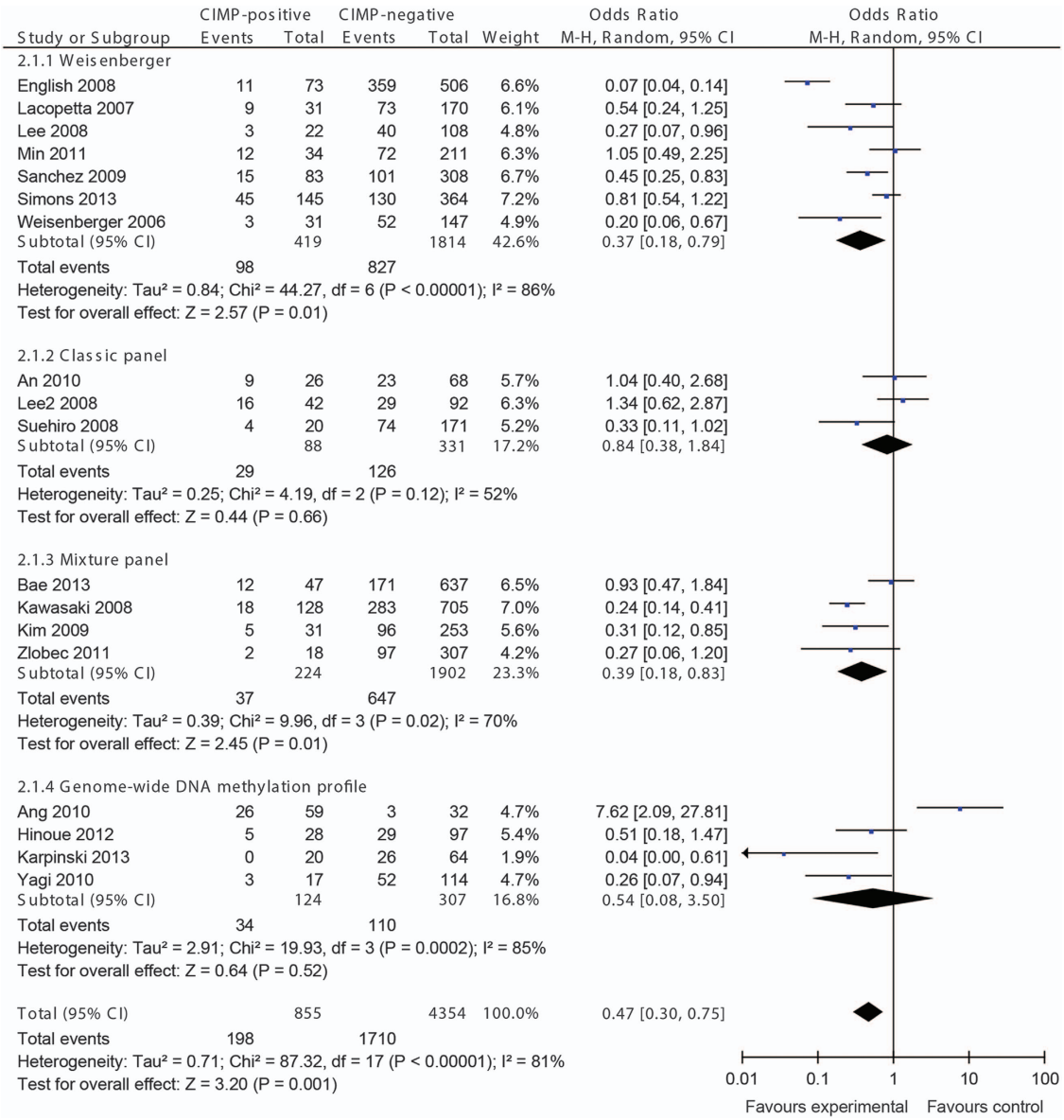

Figure 4 Meta-analysis investigating the frequency of *KRAS* mutations in CpG island methylator phenotype (CIMP)-positive vs. -negative colorectal cancers (CRCs). Random effect meta-analysis showed less *KRAS* mutations in CIMP-positive CRCs. CI, confidence interval.

Subgroup analyses of some potential confounding factors. To analyze the potential confounding factors that might influence the data collection, we performed subgroup analyses. However, because of lack of information or insufficient data, we could only conduct the subgroup analyses of methods of tissue preservation and sources of patients for *BRAF* and *KRAS* mutations, and MSI within the Weisenberger panel (Supplementary Figures S7 online). Heterogeneous results were found to exist in analysis of *KRAS* mutations, but not in those of *BRAF* mutations or MSI. First, it was found that CIMP-negative CRCs in cryopreservation groups were frequently associated with *KRAS* mutations, whereas those in formalin-fixed, paraffin-embedded (FFPE) group were not (Supplementary Figure S8 online). Second, in the subgroup analysis of case–control study vs. population-based study, only case–control studies showed that there was an association between *KRAS* mutations and CIMP-negative CRCs (Supplementary Figure S11 online). These data suggest that methods of tissue preservation and sources of patients might increase the heterogeneity of molecular studies of CIMP.

DISCUSSION

In this study, we aimed to review the data from the published studies in order to estimate the association between CIMP and other molecular incidents or clinicopathological features in CRCs. We found a trend toward more *BRAF* mutations and

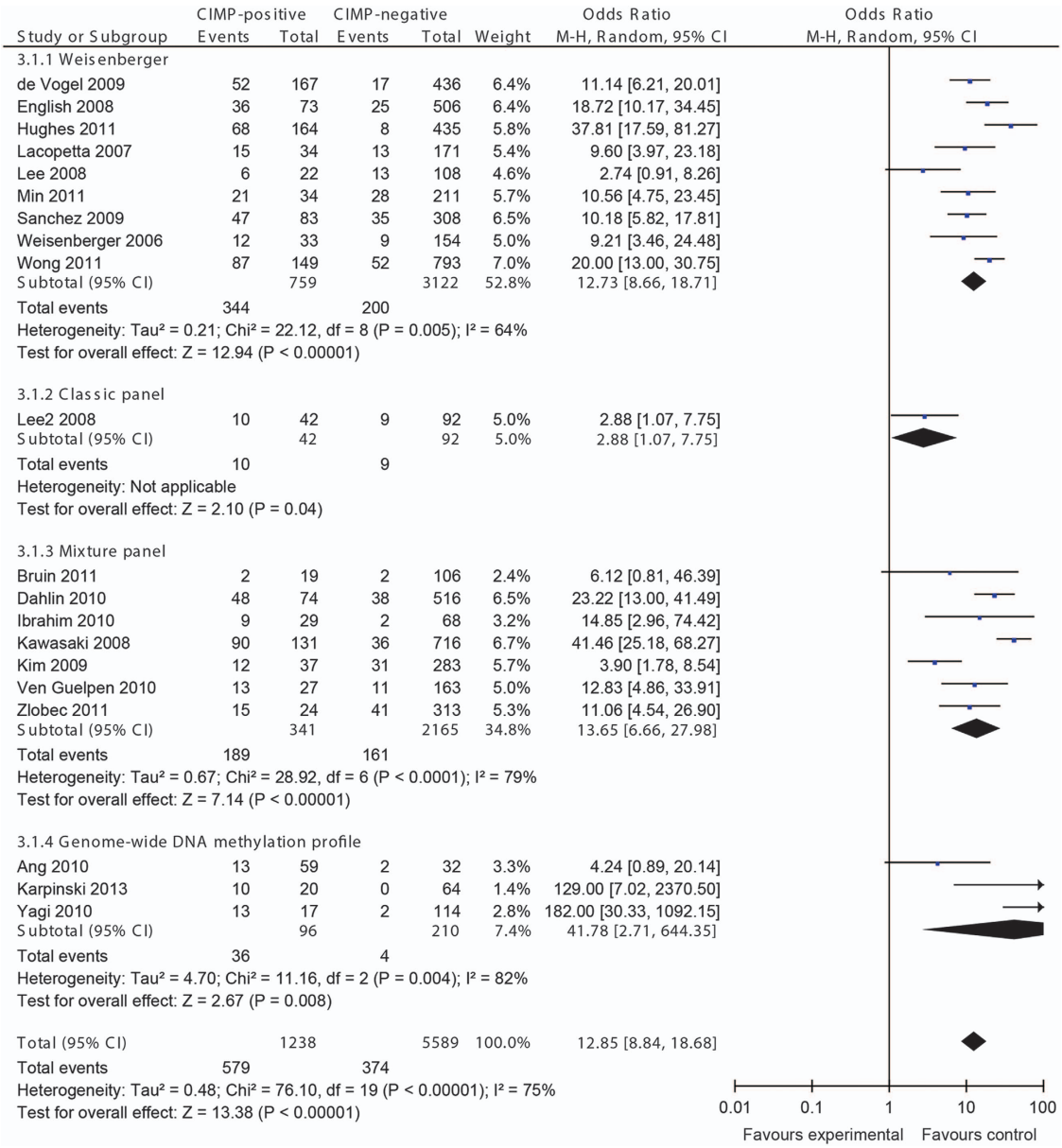

Figure 5 Meta-analysis investigating the frequency of microsatellite instability (MSI) in CpG island methylator phenotype (CIMP)-positive vs. -negative colorectal cancers (CRCs). Random effect meta-analysis showed more MSI in CIMP-positive CRCs. CI, confidence interval.

MSI and less *KRAS* mutations in CIMP-positive CRCs than CIMP-negative CRCs. We also clearly demonstrated that CIMP-positive CRCs had female preference and age dependence. Moreover, this subtype of tumors showed a significant correlation with proximal location, mucinous histology, and poor differentiation. Surprisingly, CIMP did not show a correlation with tumor stage, but was significantly associated with shorter overall survival, suggesting CIMP could be used as an independent prognostic marker.

One of the major confounding factors in the systematic review on topics relating to CIMP was the lack of a standardized definition of CIMP. Gene-specific methylation markers and genome-wide DNA methylation profile were the two major methods used to define the CIMP in CRCs. Depending on the number and set of genes used for the determination of the CIMP status, a relatively higher heterogeneity can be caused mainly by different panels of CIMP markers compared with genome-wide DNA methylation profile. Till now, two different panels of CIMP markers as well as a mixture of both were widely used in a variety of studies for CRCs. To limit most of the heterogeneity among studies, we screened and only included the studies either using the two panels of CIMP markers or a mixture of these two panels or genome-wide DNA methylation profile. In addition, subgroup analyses of different methodologies and different panels were performed.

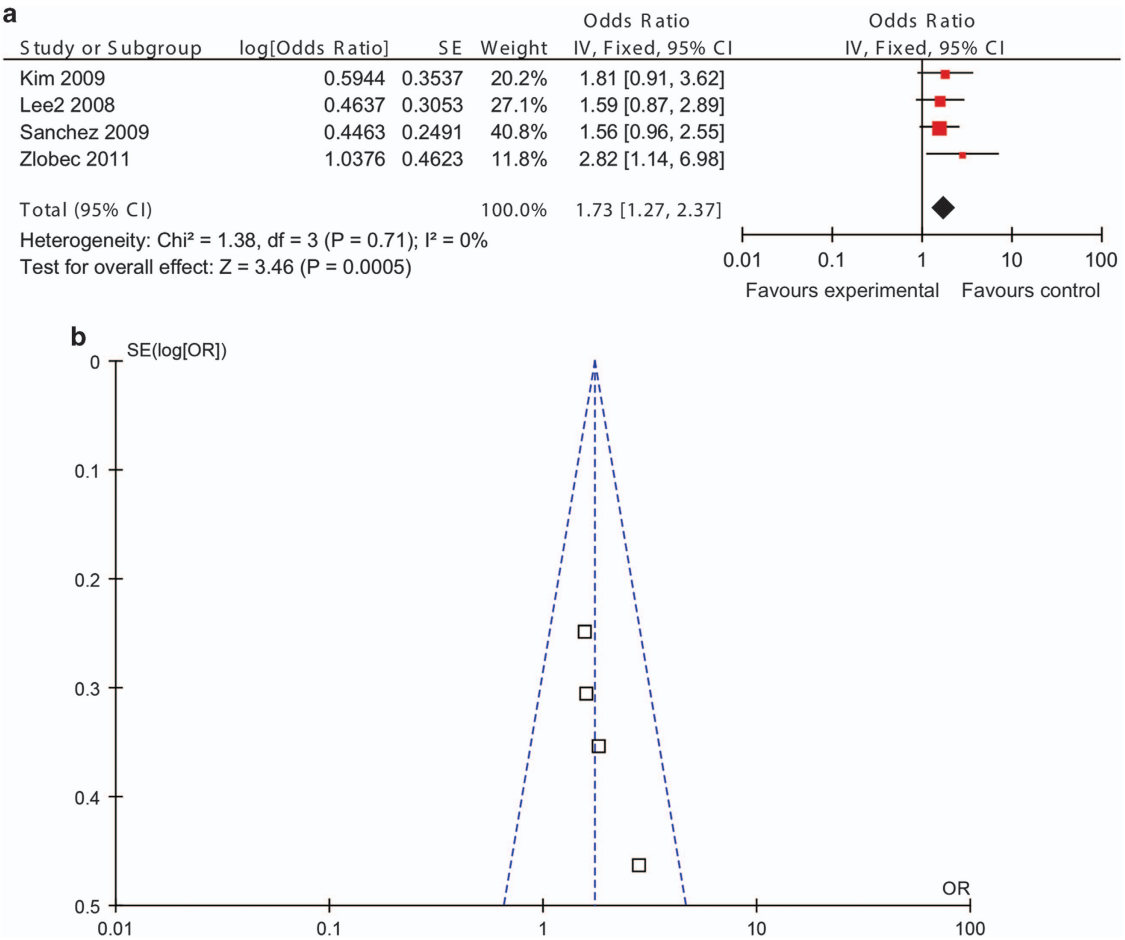

Figure 6 Meta-analysis investigating overall survival in CpG island methylator phenotype (CIMP)-positive vs. -negative colorectal cancers (CRCs). (**a**) Meta-analysis showed shorter overall survival in CIMP-positive CRCs. (**b**) Funnel plot showed that no heterogeneity existed among four included studies. CI, confidence interval; OR, odds ratio.

After the concept of CIMP was initially described in CRCs, other human tumors like glioma, paraganglioma, and gastric cancer were also characterized with similar phenotype. In gliomas, Xu *et al.*[40] revealed that *IDH1* and *IDH2* gene mutations led to CIMP by reducing the α-ketoglutarate and accumulating 2-hydroxyglutarate that could inhibit histone demethylases and the *TET* family of 5-methylcytosine hydroxylases. In paragangliomas, Letouze *et al.*[41] reported that *SDH* mutation was a key factor in causing CIMP by interplaying between the Krebs cycle and 2-oxoglutarate-dependent (2-OG) histone and DNA demethylases. For gastric cancers, Kim *et al.*[42] demonstrated an association between CIMP and oncogene mutations. In this analysis, we clearly showed that *BRAF* mutation was associated with CIMP in CRCs. In addition, in a recent study, Fang *et al.*[43] provided the first demonstration that a *BRAF*/*MEK*/*ERK* signaling pathway, which mediates silencing of *MLH1*, is more generally responsible for CIMP.

In a subgroup analysis, we found that genome-wide methylation profile-defined CIMP subset of CRCs encompassed all of the *BRAF*-mutated CRCs, whereas other 3 panels of makers only showed 61.7–83.3% *BRAF* mutations in CIMP-positive CRCs. *BRAF*/*MEK*/*ERK* signaling pathway could explain the internal mechanism of CIMP. However, in our study, ~49.8% of CIMP-positive CRCs lacked *BRAF* mutations. We speculated that the subtype of CIMP-positive CRCs without *BRAF* mutations might be caused by the effect of the microbiome. A recent study by Tahara *et al.*[44] introduced the notion that fusobacterium enrichment was associated with CIMP-positive CRCs. However, they did not find an association between fusobacterium enrichment and *BRAF* mutations, suggesting microbiome might induce CIMP through different mechanisms.

Our results demonstrated CIMP-positive CRCs were associated with proximal location, arguing for a potentially distinct molecular pathway between proximal and distal CRCs. At least two distinct pathways, the serrated pathway and the conventional pathway, underlie most CRCs.[45] The CRCs in the serrated pathway have a predilection for frequent *BRAF* mutations, MSI, and proximal location. On the contrary, the conventional pathway mostly occurs in the distal location with *KRAS* mutations and microsatellite stability. Combined with our findings, we speculated that CIMP might be a signature of the serrated CRCs.

Consistent results among different methodologies or different panels were achieved in most of the subgroup analyses,

suggesting that the heterogeneity of the present four different definitions of CIMP was limited. However, there were still some exceptions in the subgroup analyses of *KRAS* mutations, gender, and age. For analysis of *KRAS* mutation rates, the overall effects of the classic panel that included three studies and the genome-wide DNA methylation profile that included four studies did not show any differences between CIMP-positive and -negative CRCs. We believe this discrepancy between the Weisenberger panel/mixture panel and the classical panel/genome-wide DNA methylation profile was caused by a relatively limited sample size in these two subgroups, because the total weights of the two were 17.2 and 16.8%. Similarly, the overall effects of the classic panel, including three studies in analysis of gender, and the mixture panel, including three studies in analysis of age, showed heterogeneous results, and their total weights were 6.0 and 21.1%.

Regardless of the different definition of CIMP, still many confounding factors such as methods of tissue preservation, sources of patients, smoking history, publication bias, and ethnicity might prevent us from reaching a more precise conclusion.[46] We do find that whether the *KRAS* gene mutation rate is linked to negative CIMP depends on the tissue preservation methods and the sources of patients. However, tissue preservation and sources of patients did not affect the detection accuracy of the associations of *BRAF* mutations and MSI with positive CIMP. We speculate that the discrepancy might be caused by the limited sample size and the internal heterogeneity among studies, because when the negative data on the association of CIMP-negative CRCs with *KRAS* gene mutations were observed in formalin-fixed paraffin-embedded or population-based subgroups, a significant heterogeneity existed.

In summary, the meta-analysis highlights that CIMP-positive CRCs take their own molecular (especially overlapping with *BRAF* mutations) and clinicopathological features and worse prognosis from CIMP-negative CRCs, suggesting CIMP could be used as an independent prognostic marker for CRCs.

CONFLICT OF INTEREST

Guarantor of the article: Duonan Yu, MD, PhD.
Specific author contributions: Liang Zong, Duonan Yu, and Wei-Guo Zhu designed the study; Liang Zong and Masanobu Abe collected and analyzed the data; Liang Zong and Jiafu Ji interpreted the data; Liang Zong drafted the manuscript; Duonan Yu, Wei-Guo Zhu, and Jiafu Ji revised the manuscript.
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Potential competing interests: None.

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Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ CpG island methylator phenotype (CIMP) was first identified in colorectal cancers (CRCs). CRCs can be categorized into CIMP-positive and -negative subtype or CIMP-high, -low, and -negative subtype.
- ✓ It has been found that CIMP-positive or CIMP-high CRCs have a close association with molecular and clinicopathological features and prognosis, but so far different definitions of CIMP make the data controversial.

WHAT IS NEW HERE

- ✓ In this meta-analysis, we found a trend toward more *BRAF* mutations and MSI and less *KRAS* mutations in CIMP-positive CRCs than CIMP-negative CRCs. Subgroup analysis showed only the genome-wide methylation profile-defined CIMP subset encompassed all *BRAF*-mutated CRCs.
- ✓ In addition, CIMP-positive CRCs had female preference and age dependence. Moreover, CIMP-positive tumors showed a significant correlation with proximal location, mucinous histology, and poor differentiation. Surprisingly, CIMP was significantly associated with shorter overall survival, although it did not show a correlation with tumor stage, suggesting CIMP could be used as an independent prognostic marker.

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