Research Square

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The Predictive Value of CHFR Methylation for Chemotherapy Response and Prognosis in Cancer Patients: a Systematic Review and Meta-analysis

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Research Article

Keywords: CHFR, methylation, chemotherapy response, prognosis

Posted Date: March 16th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1417277/v1

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Abstract

Purpose: CHFR (checkpoint with FHA and RING finger) methylation is a promising biomarker of treatment response and cancer prognosis, whereas the predictive role of it remains controversial. Thus, this meta-analysis aimed to quantify the predictive impact of this biomarker in cancer patients.

Methods: PubMed, Embase, Cochrane Library and ClinicalTrials.gov. were searched to identify studies that assessed the association between CHFR methylation and clinical outcomes in patients with cancer. Treatment response was the primary endpoint, and overall survival (OS) and recurrence were the secondary endpoints.

Results: Thirteen studies with 2185 cancer patients met the inclusion criteria were included. Our study showed that CHFR methylation was not associated with the chemotherapy response (odds ratio = 0.93, 95% confidence interval [CI]: 0.38–2.31, P =0.88). As for OS, we found no statistically significant association either (hazard ratio [HR] = 1.14; 95% CI: 0.86–1.50, P = 0.36), except in patients treated with surgery alone (HR = 1.37; 95% CI: 1.06-1.77, P = 0.02). Moreover, CHFR methylation was significantly associated with recurrence (HR = 2.01; 95% CI: 1.25–3.25, P=0.004).

Conclusion: Our study indicates that CHFR methylation cannot be a predictive factor for response to chemotherapy, but might be a biomarker of OS and recurrence in cancer patient. Future studies should be conducted to reduce confounding and explore the mechanism.

Introduction

Epigenetic abnormalities are widespread in malignant tissues and play a key role in the occurrence, development and prognosis of many cancers[1]. CHFR (checkpoint with FHA and RING finger) is an early mitotic checkpoint gene locating at chromosome 12q24.33[2], which delays the entry into metaphase in response to mitotic stress induced by microtubule inhibitors such as paclitaxel[3] and prevents errors in chromosome segregation[4]. Cells that do not express CHFR could bypass mitotic arrest and might be sensitive to microtubule inhibitors, with subsequent cell death resulting from impaired checkpoint function. And promoter CpG island methylation is the most common change leading to CHFR inactivation[2]. Thus, assessing the methylation of CHFR in cancer patients and its potential biological effects have attracted great attention in the past two decades.

Numerous studies have reported the relationships between CHFR methylation and response to treatments, recurrence, and survival parameters[5–9]. Despite these appealing prospects, the consistency of the predictive impact of CHFR methylation remains unclear. Possible explanations may include the heterogeneity of various cancers, different sample sizes and races, the variability between sampling location, and use of diverse treatments among others. Thus, this study aimed to use meta-analytic techniques to appraise the response to chemotherapy and prognostic value of CHFR methylation in cancer.

Materials And Methods

Search strategy and selection criteria

We systematically searched PubMed, Embase, Cochrane Library and ClinicalTrials.gov by using the combinations of the following keywords: "checkpoint with forkhead and ring finger domains", "CHFR", "RNF116", "RNF196", "CHFR protein, human", "methylation", "DNA methylation". The search was updated before July 6, 2021. We also examined the bibliographies in selected articles to identify other relevant studies.

Two authors conducted the literature search and study selection independently, and a consensus was reached for any inconsistencies via a group discussion. Included studies in this meta-analysis should meet the following criteria: (1) an original human clinical trial on association between CHFR methylation and cancer; (2) the study reported at least one of following outcomes: chemotherapy response or prognosis; (3) for response, the study should provide sufficient data to calculate the odds ratio (OR) and 95% confidence intervals (CIs). And for survival parameters, the study should give hazard ratio (HR) and 95% CIs directly or report clear Kaplan–Meier curves or other information can calculate the HR and associated statistics. If two articles reported duplicate data, the more complete one was included in the meta-analysis.

Data collection and quality assessment

Data were extracted independently by two authors from qualified articles using a standardized form. We extracted the following information: name of first author, publication year, countries, ethnicity of subjects, number of samples, disease type, tumor stage, treatment, sampling location, methylation detection methods. Chemotherapy response was the primary outcome, we extracted the number of CHFR methylation and unmethylation patients in the response and nonresponse group. Overall survival (OS) and recurrence were the secondary endpoints, the HRs and corresponding 95% CI were extracted via multivariable analyses. Otherwise, we used the Excel spreadsheet and the Engauge Digitizer software version 10.6 to reproduce data in the survival curves[10]

We used the Newcastle–Ottawa scale (NOS) to evaluated the study quality based on three subscales: selection (four items), comparability (one item), and outcome (three items), which is validated for evaluating the quality of observational studies and quite comprehensive. The quality assessment was conducted independently by the same author, and any differences were reviewed and adjudicated by another author referring to the original study. Each study with NOS scores < 7 were considered as low-quality studies, whereas studies with NOS scores ≥ 7 was considered as a high-quality study. The quality assessment results of the included studies are summarized in Supplemental 1.

Statistical analyses.

All analyses were conducted using Review Manager 5.3 and Stata 14.0 statistical software. We used I squared (I^2) tests based on Q tests to assess potential heterogeneity[11]. Significant heterogeneity was defined when $P < 0.05$ or $I^2 > 50\%$. When observed significant heterogeneity, we used random effects model[12] to calculate OR and HR, otherwise, applied fixed effects model[13]. In order to detect potential sources of heterogeneity, we performed meta-

regression analysis and subgroup analyses stratified by ethnicity, sample size, treatment and sampling location. To investigate the stability of the results, sensitivity analysis was performed by omission of each single study[14]. Publication bias was assessed by using a method reported by funnel plot. All P values are two sided, and P values < 0.05 were considered statistically significant.

Results

Qualified study characteristics

Through the database search, 303 articles were identified for initial evaluation (Fig. 1), and of these, 165 were excluded, which included duplicates and irrelevant topics. A total of 138 potentially eligible studies were selected. After detailed evaluations, 125 studies were excluded due to wrong biomarkers, duplication, or other reasons. Ultimately, 13 studies that included 2185 patients met the inclusion criteria and were used in the meta-analysis[5, 7–9, 15–23]. The characteristics of the included studies are presented in Table 1.

Table 1
Major features of the included studies

Author Year	Design	Country	Race	Size	Disease	Tumor stage	Treatment	F s
Cha Y 2019[5]	retro	Korea	Asian	102	CRC	metastatic	Irinotecan-Based Chemotherapy	t
Hamilton JP 2006[15]	pro	USA	White/African American	35	Esophageal Carcinogenesis	II-III	Cisplatin + 5-FU + x-ray radiation	t
Koga Y 2006[16]	retro	Japan	Asian	12	GC	advance/recurence	prior chemotherapy + TXT/TXL	t
NCT01715233 2019[18]	pro	USA	White/African American	18	Esophageal, Gastroesophageal, GC	metastatic	DOC + Leucovorin + Fluorouracil + Cisplatin	N
Ogi K 2005[20]	retro	Japan	Asian	13	OSCC	II-IV	DOC + CDGP(nadaplatin)	t
Wang M 2014[17]	retro	China	Asian	117	GC	advanced	paclitaxel + capecitabine/cisplatin + capecitabine	t
Yoshida K 2006[19]	retro	Japan	Asian	41	GC	advance/recurence	Paclitaxel/ DOC + S-1	t
Cleven A H 2014[23]	retro-study/validation	Netherlands	Caucasian	628	CRC	I-IV	surgery	t
Gao L 2016[7]	retro	China	Asian	358	AML	NA	DA/MA/Allo-HSCT/auto-HSCT	b r
Koga T 2011[8]	retro	Japan	Asian	208	NSCLC	I-IV	surgery	t
Li Y 2015[21]	pro	China	Asian	94	GC	I-IV	surgery + DOC	t
Salazar F 2011[9]	retro	Spain	Caucasian	308	NSCLC	IV	second-line chemotherapy/TKIs/none	s
Sacristan R 2014[22]	retro	Spain	Caucasian	251	Bladder Cancer	pTaLG/pT1LG/pT1HG	NA	t

GC: gastric cancer CRC: colorectal cancer AML: acute myeloid leukemia NSCLC: non-small cell lung cancer OS: overall survival DA: daunorubicin and cytarab cytarabine OSCC: Oral squamous cell carcinoma DOC: docetaxel TKIs: tyrosine kinase inhibitors MSP: methylation-specific polymerase chain reaction COBR analysis MS-MLPA: MS, multiplex, ligation-dependent, probe-amplification assay

Response to chemotherapy

A total of 7 articles, including 338 patients were used to assess the association between CHFR methylation and response to chemotherapy[5, 15–20]. Our results indicated that DNA methylation of CHFR is not a predictor of the response to chemotherapy in cancer (OR = 0.93, 95% CI: 0.38–2.31, P = 0.88; Fig. 2). Slight heterogeneity was observed in the magnitude of the effect across the studies (I^2 = 52%; P = 0.05). To explore the source of heterogeneity, a subgroup analysis was conducted by race, sample size (median size was 35) and treatment. The results of these subgroup analysis showed that CHFR methylation was not associated with chemotherapy response in all subgroups (Table 2). Moreover, the results of the sensitivity analyses found that the conclusion was not altered by sequentially excluding an individual study (Fig. 3). The funnel plot assessed potential publication bias and indicated the studies might be some publication bias (Fig. 4).

Table 2
Subgroup analysis and meta-regression of the studies reporting the association of CHFR methylation and response to chemotherapy in cancer.

			ORs 95% CI			Heterogeneity	
Stratified analysis	No. of studies	No. of patients	Fixed	Random	Meta-regression P-value	I²(%)	P-value
Race					0.352		
Asian	5	309	1.15(0.66, 1.99)	1.25(0.42, 3.69)		60	0.04
White/African American	2	53	0.34(0.08, 1.46)	0.37(0.08, 1.69)		0	0.37
Size					0.88		
≤ 35	4	78	0.96 (0.36, 2.59)	1.11 (0.19, 6.68)		51	0.11
35	3	260	0.96 (0.53, 1.74)	0.89 (0.28, 2.84)		69	0.04
Treatment					0.88		
Microtubule inhibitor	5	143	0.99 (0.51, 1.95)	1.09 (0.31, 3.87)		57	0.05
Other chemotherapy	3	195	0.96 (0.44, 2.09)	0.94 (0.28, 3.12)		49	0.14

Overall survival

A total of 6 studies involving 1698 patients were included to evaluate the association between CHFR methylation and OS[5, 7–9, 21, 23]. Among them, two studies[21, 23] each reported two different groups of people, so we included them as four separate studies, resulting in an analysis of 8 groups eventually. The summary of the HRs has shown that cases with CHFR methylation might be associated with a shorter OS, but not statistically significant (HR = 1.14; 95% CI: 0.86–1.50, P = 0.36; Fig. 5). The results of subgroup analysis showed that CHFR methylation was only associated with a poorer OS in patients treated with surgery alone (HR = 1.37; 95% CI: 1.06–1.77, P = 0.02) (Table 3). The sensitivity analysis indicated the omission of individual studies did not significantly change the pooled HR of OS (Fig. 6). The funnel plot indicated potential publication bias in current meta-analysis (Fig. 7).

Table 3
Subgroup analysis and meta-regression of the studies reporting the association of CHFR methylation and overall survival.

			HRs 95% CI			Heterogeneity	
Stratified analysis	No. of studies	No. of patients	Fixed	Random	Meta-regression P-value	I²(%)	P-value
Race					0.943		
Asian	5	762	1.20 (0.92, 1.56)	1.09 (0.60, 1.97)		72	0.007
Caucasian	3	936	1.11 (0.92, 1.34)	1.13 (0.89, 1.43)		32	0.23
Size					0.337		
184	4	356	0.96 (0.70, 1.33)	0.87 (0.50, 1.52)		60	0.06
184	4	1342	1.20 (1.01, 1.43)	1.30 (0.93, 1.80)		65	0.04
Treatment					0.428		
surgery	3	836	1.37 (1.06, 1.77)	0.89 (0.70, 1.14)		0	0.49
chemotherapy	2	410	0.89 (0.70, 1.14)	0.92 (0.39, 2.16)		73	0.02
surgery + chemotherapy	3	452	1.30 (0.95, 1.78)	1.14 (0.86, 1.50)		60	0.02
Sample region					0.923		
Tissue	6	1032	1.17 (0.94, 1.45)	1.11 (0.74, 1.69)		62	0.02
Bone marrow/Serum	2	666	1.11 (0.90, 1.38)	1.16 (0.73, 1.84)		76	0.04

Recurrence

Only 2 studies involving 467 patients evaluated the association between CHFR methylation and cancer recurrence[8, 22]. Pooled analysis results have indicated that patients with CHFR methylation show a significantly high recurrent risk (HR = 2.01; 95% CI: 1.25–3.25, P = 0.004; Fig. 8)

Discussion

CHFR as a classical cell cycle checkpoint regulator has been reported that hypermethylation and inactivation of CHFR promoter region was found in several types of malignancy, including not only solid cancers[24–29], but also hematological malignancies[30–32]. Among these, digestive system carcinomas and non-small cell lung cancer were extensively studied, and several meta-analysis and system reviews[33–36] indicated that CHFR promoter methylation could serve as a diagnostic biomarker for cancer and a promising molecular target for therapy. However, due to the conclusion of the predictive role of CHFR methylation in chemotherapy response and prognosis are still inconsistent and controversial, we conducted a comprehensive meta-analysis to achieve further insight into these associations.

Since impairment of CHFR can cause the fast entry from prophase into metaphase, it might be a reason for the sensitivity to chemotherapeutic drugs, especially microtubule inhibitors[6]. And based upon the strong preclinical correlation between CHFR methylation and taxane sensitivity[37–41], it is rational to utilize CHFR methylation status as a molecular marker to select patients with indications for chemotherapy. But in our study, we verified that no correlation was found between CHFR methylation and chemosensitivity in clinical cohorts, wholly or partially. And one included study[19] even favored that the unmethylation group in advanced and recurrent gastric cancer might benefit from taxane treatment. In contrast to cells, the more extensive heterogeneity among tumor samples may be one of possible explanations for the inconsistencies between our current results and studies *in vitro*. Moreover, taxane is reported to be effective even if CHFR is expressed[19], suggesting that other molecules are associated with the chemoresistance and CHFR methylation alone may not be informative enough as a predictor of response to chemotherapy. In this part, included studies mainly focused on digestive system carcinomas, most with gastric cancer. As for other cancer types, only one article[42] assessed the chemosensitivity-related aberrant methylation in 24 patients with non-small cell lung cancer, but failed to detect CHFR methylation and then was not included. So, further studies with other cancer patients are needed. In addition, the median sample size of studies is 35, and the response assessment criteria were various or not reported, indicating larger sample sizes with the unified standard will be essential to corroborate our findings.

Effective prognostic biomarkers can help to identify patients with risk of poor outcomes or recurrence, and guide treatment stratification and intensified surveillance. Although OS showed a trend favoring the CHFR unmethylation group in the present study, the difference in OS based on CHFR methylation status was not apparent (P = 0.036). Only in subgroup analysis grouped by treatment, a strong positive association between CHFR methylation and poor OS was observed in patients treated with surgery alone (HR = 1.37; 95% CI: 1.06–1.77, P = 0.02), given the possible contribution that loss of CHFR function might make towards cancer progression[43]. By contrary, there is one group[21] in the meta-analysis showed OS was longer in docetaxel-treated gastric cancer patients with CHFR methylation. We speculate that alternation of microtubule inhibitors sensitivity may contribute to the protective role of CHFR methylation in gastric cancer. Therefore, the correlation between CHFR methylation and OS might be more evident if subsequent studies evaluate a more homogeneous population. And based on two studies, we also determined the significant association between CHFR methylation and cancer recurrence. In addition, Cha et al[5] found that CHFR methylation was predictive of time-to-progression in patients with metastatic colorectal cancer treated with irinotecan-based systemic chemotherapy. So, other treatment outcomes also need to be studied further.

Besides those mentioned above, the present meta-analysis has some other limitations: (1) substantial heterogeneity among the studies on CHFR methylation and chemotherapy response or OS was not fully addressed by subgroup analysis; (2) we included studies that reported univariate HR which could introduce a bias toward both the overestimation of the prognostic roles of CHFR methylation and multivariate HR; (3) funnel plot exhibited potential publication bias for the analysis.

In summary, we conclude that CHFR methylation cannot predict the response of cancer to chemotherapy, but might be a biomarker of prognosis. Future studies should be conducted to reduce confounding and explore the mechanism.

Declarations

Availability of data and materials

All data generated or analysed during this study are included in this published article and its supplementary information files.

Competing interests

The authors declare that they have no competing interests.

Funding

This study was supported by grants from the National Key R&D Program of China (no. 2016YFC0904900), National Science and Technology Major Projects for “Major New Drugs Innovation and Development” (no. 2018ZX09201014, no. 2017ZX09101001 and no. 2017ZX09304028), National Natural Science Foundation of China (no. 81872940, 81973395 and 82073935) and Beijing Natural Science Foundation (no. 7171012).

Authors' contributions

ZZ and ZWJ have made substantial contributions to conception and design of the study; XQ searched literature, extracted data from the collected literature; LQX analyzed the data; ZHX and ZXD wrote the manuscript; CYM revised the manuscript; All authors have reviewed and approved the manuscript prior to submission.

Acknowledgements

We thank the reviewers whose comments and suggestions improved this manuscript.

Consent for publication

Not applicable.

Ethical statement

Not applicable.

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Figures

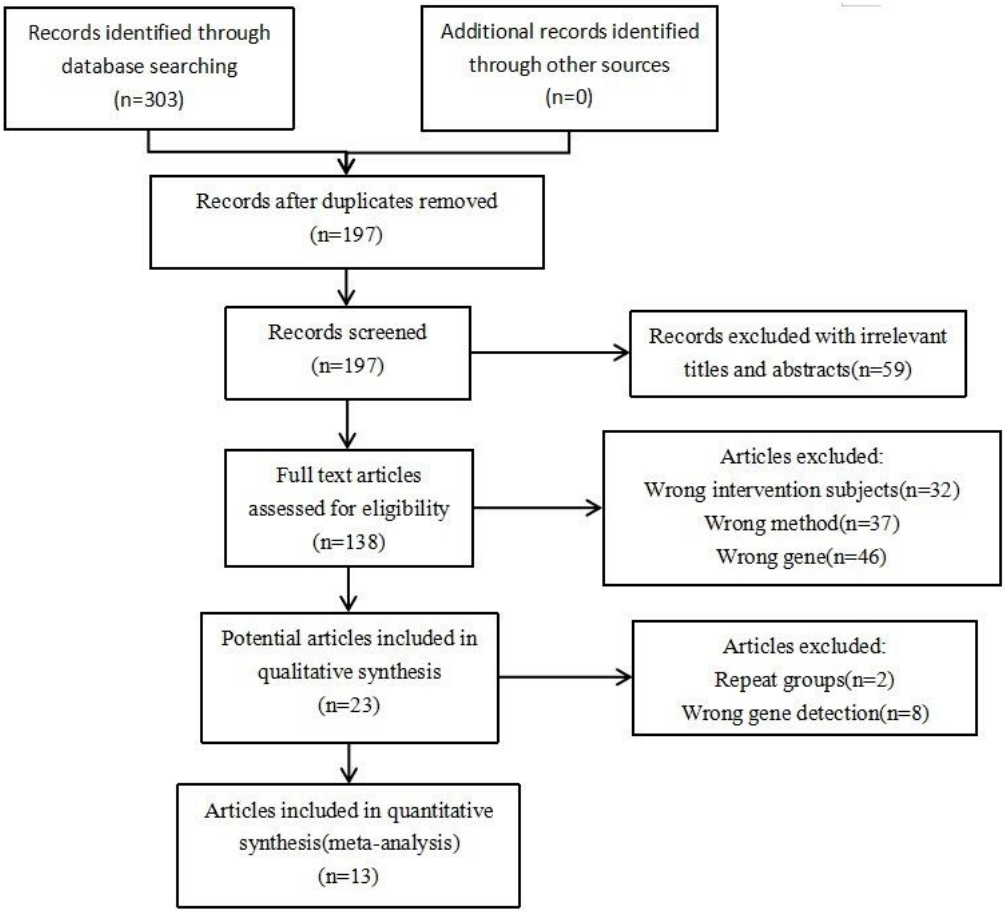

Figure 1

Flow diagram of study inclusion.

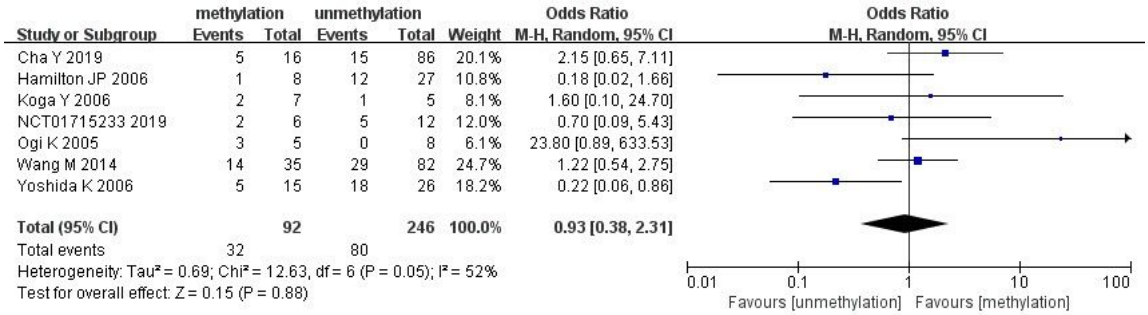

Figure 2

Forest plot for pooled OR and the corresponding 95% CI of CHFR methylation for response to chemotherapy of cancer patients.

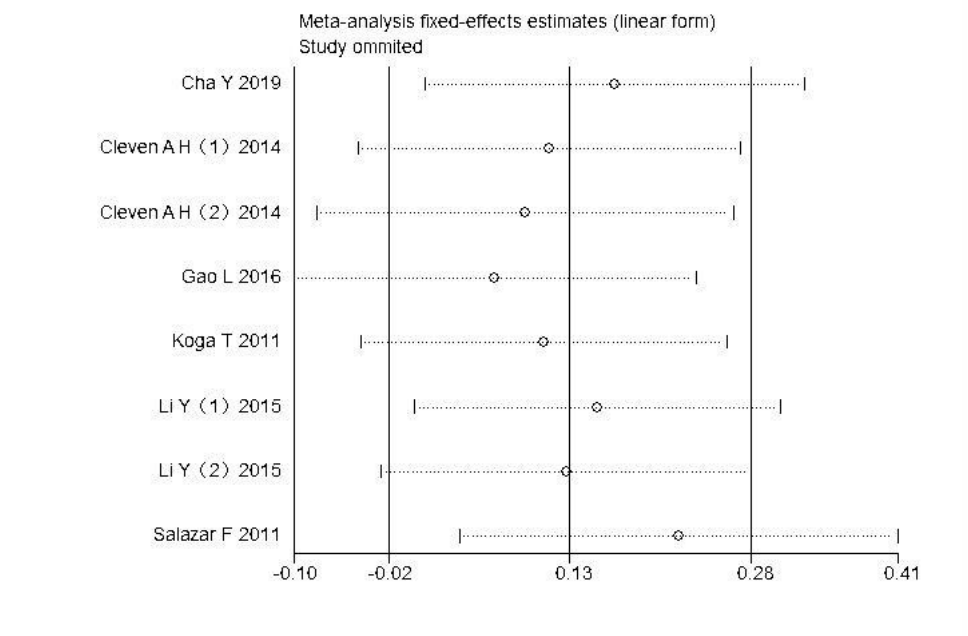

Figure 3

Sensitivity analysis of pooled ORs of CHFR methylation for response to chemotherapy of cancer patients.

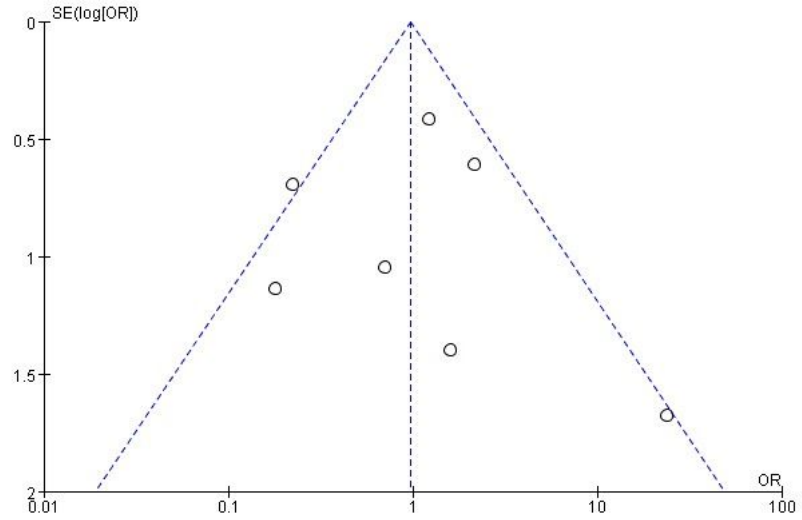

Figure 4

Funnel plot of ORs of CHFR methylation for response to chemotherapy of cancer patients.

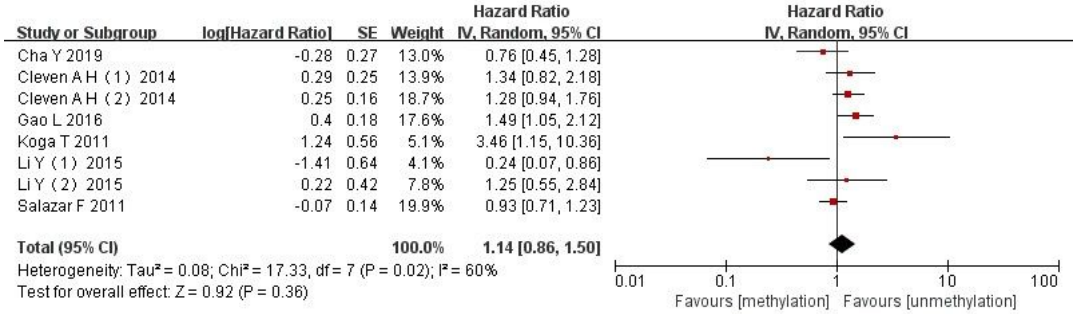

Figure 5

Forest plot for pooled HR and the corresponding 95% CI of CHFR methylation for OS of cancer patients.

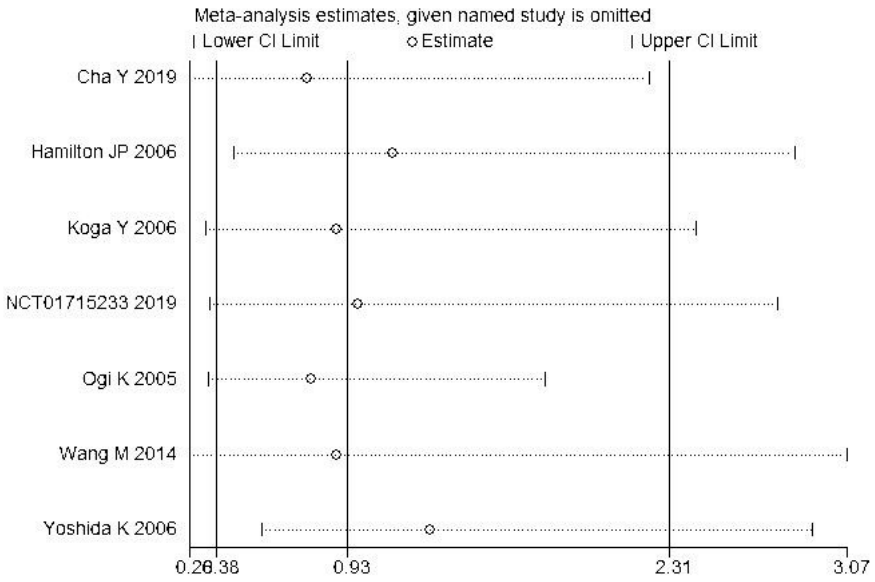

Figure 6

Sensitivity analysis of pooled HRs of CHFR methylation for OS of cancer patients.

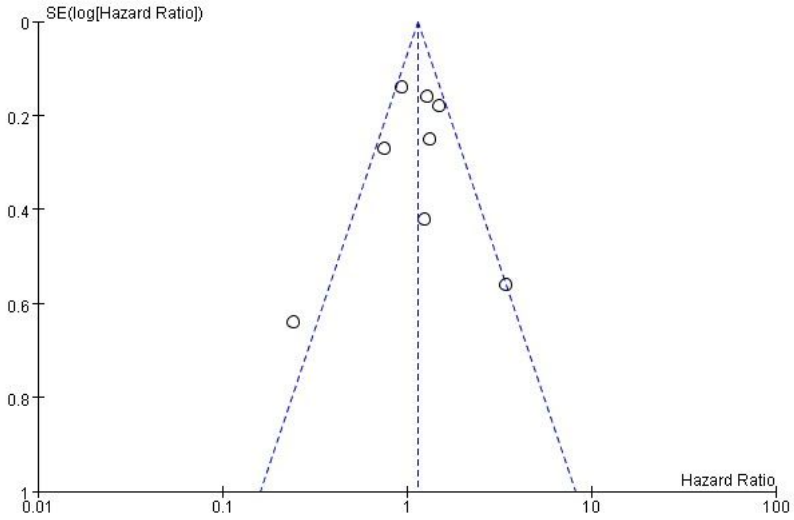

Figure 7

Funnel plot of HRs of CHFR methylation for OS of cancer patients.

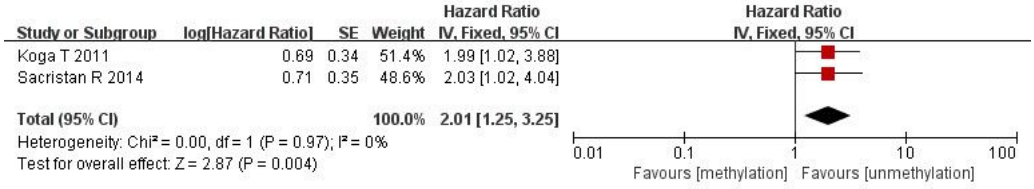

Figure 8

Forest plot for pooled HR and the corresponding 95% CI of CHFR methylation for recurrence of cancer patients.

Supplementary Files

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- Supplemental1.docx