Int J Clin Exp Med 2018;11(1):43-58
www.ijcem.com /ISSN:1940-5901/IJCEM0059820

Review Article

Prognostic value of circulating and disseminated tumor cells in ovarian cancer: a meta-analysis

Xiaofang Han[1], Aiming Wang[2], Yaqin He[3], Xiaocheng Wang[4]

[1]Departments of Reproduction, Shanxi Provincial People's Hospital, Taiyuan 030012, Shanxi Province, China; [2]Department of Reproduction, Navy General Hospital, Beijing, China; [3]Department of Information Management, Shanxi Center for Disease Control and Prevention, Taiyuan, Shanxi Province, China; [4]Department of Medical Record & Statistics, Shanxi Provincial People's Hospital, Taiyuan 030012, Shanxi Province, China

Received February 24, 2017; Accepted December 4, 2017; Epub January 15, 2018; Published January 30, 2018

Abstract: Objective: The prognostic values of circulating tumor cells (CTCs) in peripheral blood and disseminated tumor cells (DTCs) in bone marrow have been investigated in many tumors; however, they remain a source of controversy in patients with ovarian cancer. This meta-analysis aimed to assess the prognostic role of CTCs/DTCs in ovarian cancer patients. Methods: A systematic computer-based retrieval was conducted in the electronic databases of PubMed, EMBASE and Web of Science. Association of CTCs/DTCs detection with clinicopathological characteristics of ovarian cancer was summarized using the estimated odds ratio (OR). Overall survival (OS) and disease-free survival (DFS)/progression-free survival (PFS) in relation to CTCs/DTCs level in ovarian cancer were estimated by the hazard ratio (HR) with its 95% confidence interval (95% CI). Subgroup analyses were carried out to evaluate whether sampling type, detection method and treatment method would influence the prognostic values of CTCs/DTCs. Publication bias was evaluated using funnel plot and Egger's/Begg's test; meanwhile, a sensitivity analysis was performed using the leave-one-out approach. Results: A total of 16 published studies met the inclusion criteria. Results of this meta-analysis suggested that difference in incidence of tumor cells (CTCs/DTCs) was associated with CA125 (OR = 2.43; 95% CI [1.44-4.09]), FIGO stage (OR = 2.18; 95% CI [1.05-4.54]), tumor grade (OR = 1.32; 95% CI [1.03-1.69]), cancer type (OR = 0.70; 95% CI [0.52-0.94]), nodal status (OR = 0.70; 95% CI [0.51-0.98]), platinum sensitivity (OR = 2.05; 95% CI [1.03-4.07]) and ascites (OR = 2.16; 95% CI [1.43-3.27]). Furthermore, ovarian cancer patients in high CTCs/DTCs group were markedly associated with shorter OS (HR = 1.84; 95% CI [1.53-2.21]) and PFS/DFS (HR = 1.67, 95% CI [1.41-1.98]). In addition, our results indicated that OS was related to detection and treatment methods, while PFS/DFS was associated with sampling type, detection and treatment methods, as could be seen from subgroup analyses. Conclusions: It is indicated in the present meta-analysis that CTCs/DTCs are correlated with OS and PFS/DFS of ovarian cancer, which may be served as a novel biomarker in patients with early and metastatic ovarian cancer. But such result should be further confirmed in future studies.

Keywords: Circulating tumor cells, disseminated tumor cells, ovarian cancer, prognosis

Introduction

As one of the most common gynecologic malignancies with high mortality, ovarian cancer is associated with poor prognosis, with the 5-year survival rate of only 40% [1-3]. Such poor outcome can mainly be attributed to the late discovery. 75% of clinical cases are at stage III/IV when their cancers are discovered. In addition, most of those patients experience disease relapse even in the presence of aggressive cytoreductive surgery and reasonable chemotherapy [4-6]. Ovarian cancer detection contributes to reducing 1/5 of mortality. Carbohydrate antigen 125 (CA125) is the most widely used serum biomarker for ovarian cancer in clinical practice, but it does not have satisfying clinical value. Negative CA125 can be seen in half of patients with early-stage ovarian cancer; meanwhile, it can also be detected in malignant gynecological diseases, such as malignancies of the fallopian tube and endometrium [7-9]. Therefore, CA125 is not an effective marker for ovarian cancer, which has given rise to a necessity to find a sensitive and specific index facilitating the earlier diagnosis of ovarian cancer and distant metastasis prediction. Circulating tumor cells (CTCs) are tumor cells released from the primary tumors, recurrent tumors, or metastases, which are then circu-

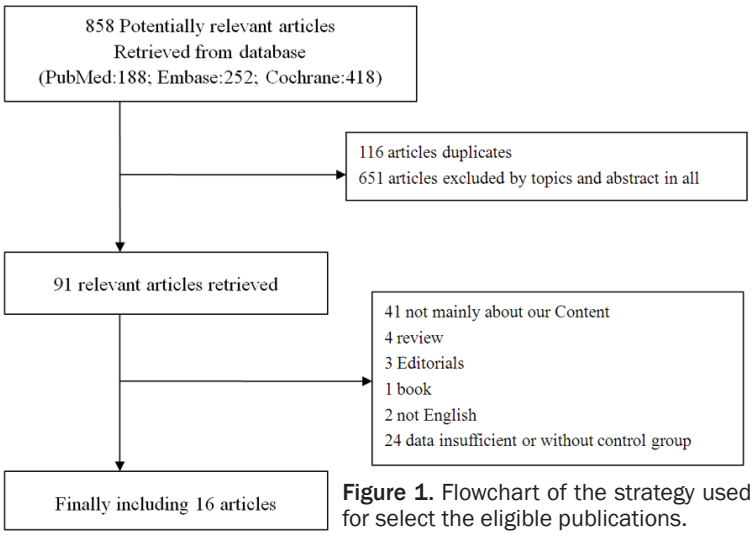


Figure 1. Flowchart of the strategy used for select the eligible publications.

lated in the peripheral blood or lymph nodes, leading to new tumor metastases. CTCs account for an important element in the process of cancer metastasis [10-12]. Disseminated tumor cells (DTCs) are tumor cells in bone marrow of patients with cancer, which can be used as a 'liquid biopsy' to obtain helpful information for individual patients [13, 14]. It has been demonstrated that both CTCs and DTCs display potentials to monitor treatment efficacy among patients with metastatic breast, prostate, and colorectal cancer [15-19]. However, the prognostic value of CTCs/DTCs in ovarian cancer is still controversial. It is found in some studies that CTCs/DTCs are not related to poor prognosis for ovarian cancer patients [20]. In contrast, other studies reveal that CTCs/DTCs are associated with poor clinical outcomes and clinicopathological characteristics in clinical treatment of ovarian cancer patients [10, 21, 22]. Given the conflicting results from previous studies, a meta-analysis was carried out in this study to investigate the prognostic value of CTCs/DTCs in OS and DFS/PFS of ovarian cancer patients. Furthermore, subgroup analyses were conducted to evaluate whether sampling type, detection method and treatment method would influence the prognostic value of CTCs/DTCs.

Methods

Search strategy

A computer-based retrieval was conducted in databases like Web of Science, PubMed and EMBASE on October 27, 2016, so as to give a systematic review. Key words were set as "ovarian cancer", "ovarian carcinoma", "ovarian neoplasms", "neoplastic cells, circulating", "circulating tumor cell (s)", "disseminated tumor cell (s)", "CTC" and "DTC". All key words were combined with "AND" and "OR". Only studies published in peer reviewed journals were included, while data from letters, books and conference abstracts were excluded. All studies were limited to human studies with English language, and citation lists of retrieved articles were checked to ensure sensitivity of the search strategy.

Inclusion and exclusion criteria

Studies were selected according to the following criteria: (1) studies with sufficient data to be collected for the prognostic value of CTCs/DTCs in ovarian cancer; (2) those with a sample size of at least 30 patients; (3) those with the objects of study of ovarian patients without any restriction on age or race; and (4) those with results containing overall survival (OS) and progress-free survival (PFS).

Studies were excluded based on the following criteria: (1) reviews, editorials, case reports, commentary articles or animal experiments; (2) laboratory studies without exact data or with data that could not be calculated from the originally published article; and (3) studies with no sufficient data to be extracted.

Quality assessment

Titles and abstracts of all the studies retrieved above were screened by two investigators independently. Full texts were retrieved for detailed evaluation according to the inclusion and exclusion criteria for records that could not be evaluated through titles or abstracts. Any disagreement was solved by discussion. Meanwhile, publication bias and sensitivity analysis were also performed to assess study quality.

Data extraction

The following details were extracted from the included studies: name of first author, sample size, sampling time, CTCs or DTCs, detection method, target antigen/target gene, cutoff defi-

Table 1. Circulating tumor cells (CTCs) and disseminated tumor cells (DTCs) clinical outcome of the eligible studies

Author	No. of patients	Sampling time	Sample	Detection methods	Markers	Cut off of CTCs	Detection rate, %	Outcome
Aktas et al. 2011	86	Pre-therapy and post-therapy	PB	RT-PCR	EpCAM, MUC-1, HER2 CA125	-	19.00%	DFS/OS
Banys et al. 2009	112	Pre-therapy	BM	ICC	A45-B/B3	≥ 1 CK cell positive	25.00%	PFS/OS
Behbakht et al. 2011	43	Pre-therapy	PB	CellSearch (ICC)	CK, EpCAM	≥ 1 cell positive	44.19%	PFS
Braun et al. 2001	108	Pre-therapy	BM	ICC	A45B/B3	≥ 1 CK cell positive	29.63%	DFS/OS
Fan et al. 2009	66	Pre-therapy	PB	Cell invasion assay	CAM/EPi	≥ 1 cell positive	65.15%	DFS/OS
Fehm et al. 2006	69	Pre-therapy	BM	IHC	A45-B/B3	≥ 1 CK cell	36.2%	-
Fehm et al. 2013	456	Pre-therapy	BM	ICC	A45B/B3	≥ 1 CK cell positive	27.40%	PFS/OS
Judson et al. 2003	64	Pre-therapy	PB	ICC	CK8 and 18 TFS-2 CK7, CK20 EGFR	≥ 1 cell positive	18.75%	DFS/OS
Kolostova et al. 2015	118	Pre-therapy	PB	CM/RT-PCR	MUC1, EpCAM, CA125	> 1 cell positive	59%	-
Kuhlmann et al. 2014	143	Pre-therapy	PB	RT-PCR	EpCAM, MUC1 or MUC16	-	13.98%	DFS/OS
Liu et al. 2013	30	Pre-therapy	PB	Cellsearch	CK, EpCAM	≥ 2 cell positive	-	DFS/OS
Marth et al. 2002[a,b]	73/90	Pre-therapy	PB/BM	ICC	MOC-31	-	12%/21%	PFS/OS
Obermayr et al. 2013	200	Pre-therapy and post-therapy	PB	RT-PCR	PPIC	-	24.00%	DFS/OS
Pearl et al. 2014	88	Pre-therapy	PB	CAM-initiated CTC enrichment	Epi, HL	iCTCs ≥ 5	82.95%	DFS/OS
Poveda et al. 2011	216	Pre-therapy	PB	CellSearch (ICC)	EpCAM/CK/CD45/DAPI	≥ 2 cell stained	14.35%	PFS/OS
Sang et al. 2014	80	Pre-therapy	PB	RT-PCR	MAGE-As	-	47.50%	OS

[a,b]Study of Marth et al. discussed both PB and BM samples of cancer patients. CTCs, circulating tumor cells; DTCs, disseminated tumor cells; PB, Peripheral blood; BM, Bone marrow; OS, overall survival; PFS, progression free survival; RT-PCR, Reverse transcription-polymerase chain reaction; ICC, immunocytochemistry; CM, cytomorphological.

Table 2. Quality assessment of included articles using the Newcastle-Ottawa scale

Author (year)	Selection	Comparability	Outcome	NOS score
Aktas et al. 2011	4	0	2	6
Banys et al. 2009	4	0	2	6
Behbakht et al. 2011	4	0	2	6
Braun et al. 2001	4	1	2	7
Fan et al. 2009	4	1	2	7
Fehm et al. 2006	4	0	2	6
Fehm et al. 2013	4	1	3	8
Judson et al. 2003	4	1	3	8
Kolostova et al. 2015	4	0	2	6
Kuhlmann et al. 2014	4	1	2	7
Liu et al. 2013	4	1	2	7
Marth et al. 2002	4	0	2	6
Obermayr et al. 2013	4	1	2	7
Pearl et al. 2014	4	0	2	6
Poveda et al. 2011	4	1	2	7
Sang et al. 2014	4	0	2	6

nition of positive CTCs, detection rate and outcome. Any disagreement between authors was settled by discussion.

Statistical analysis

Statistical analysis was performed using Stata software (version 12.0, Stata Corp, College Station, TX, USA). Association of CTCs/DTCs detection with clinicopathological characteristics of ovarian cancer was summarized using estimated odds ratio (OR). OS and DFS/PFS in relation to CTCs/DTCs level of ovarian cancer were estimated by hazard ratio (HR) with its 95% confidence interval (95% CI). HR and 95% CI were collected from the original articles directly or calculated from the available data using the method reported by Jayne F. Tierney [23]. Heterogeneity between studies was evaluated using the Cochran Q test and I^2 statistic [24]. A $P < 0.05$ and an $I^2 > 50\%$ indicated substantial heterogeneity, thus a random-effects model estimate was used; otherwise, a fixed-effects model estimate was adopted. Pooled analysis was completed by evaluating all relevant studies in accordance with different clinicopathological parameters and prognostic outcomes. Combination of HR or OR was considered to be statistically significant when $P < 0.05$. Furthermore, a meta-regression was used based on the characteristics of all included studies, so as to explore the potential sources of heterogeneity. Furthermore, subgroup analyses were also performed. Publication bias was assessed using the funnel plot and the Egger's and Begg's test. Sensitivity analysis was conducted using the leave-one-out approach, so as to assess the quality and consistency of results. Difference with $P < 0.05$ was deemed as statistically significant.

Results

Search strategy

Altogether 858 articles were identified from literature retrieval, among which 116 were duplicate, 41 were irrelevant, 4 were reviews, 3 were editorial articles, 1 was book, 2 were non-English language, and 24 had insufficient data or did not set a control group; thus they were excluded. In addition, another 651 articles were excluded by titles and abstracts. Finally, 16 studies that met the inclusion criteria were enrolled in our meta-analysis [10, 20-22, 25-36]. The flowchart of search results was presented in **Figure 1**.

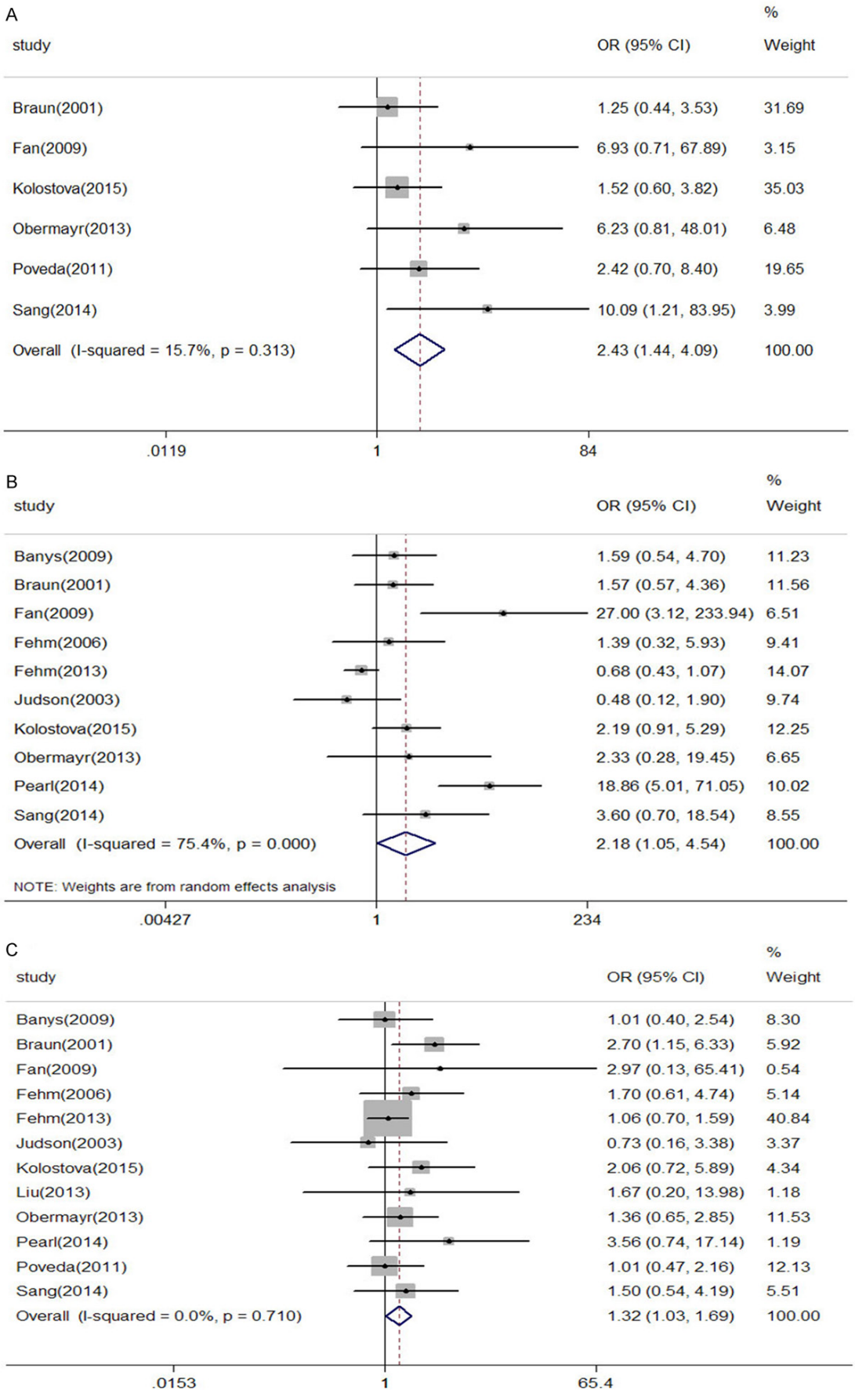
The following information of each eligible study was recorded: name of first author, sample size, sampling time, CTCs or DTCs, detection method, target antigen/target gene, cutoff definition of positive CTCs, detection rate and outcome. Details of the included studies were summarized in **Table 1**.

Quality assessment

Quality of included articles was assessed by adopting Newcastle-Ottawa Scale. 2 articles had 8 points, 6 had 7 points, and 8 had 6 points. The details were shown in **Table 2**.

Correlation of CTCs/DTCs with clinicopathological parameters

Six studies were analyzed for investigating the relationship between CTCs/DTCs and CA125 (high-expression VS low-expression) (**Figure 2A**) [10, 22, 27, 31, 34, 36]. The results indicated a remarkably higher incidence of CTCs/


A
study
OR (95% CI)
%
Weight
Braun(2001) 1.25 (0.44, 3.53) 31.69
Fan(2009) 6.93 (0.71, 67.89) 3.15
Kolostova(2015) 1.52 (0.60, 3.82) 35.03
Obermayr(2013) 6.23 (0.81, 48.01) 6.48
Poveda(2011) 2.42 (0.70, 8.40) 19.65
Sang(2014) 10.09 (1.21, 83.95) 3.99
Overall (I-squared = 15.7%, p = 0.313) 2.43 (1.44, 4.09) 100.00
.0119
1
84
B
study
OR (95% CI)
%
Weight
Banys(2009) 1.59 (0.54, 4.70) 11.23
Braun(2001) 1.57 (0.57, 4.36) 11.56
Fan(2009) 27.00 (3.12, 233.94) 6.51
Fehm(2006) 1.39 (0.32, 5.93) 9.41
Fehm(2013) 0.68 (0.43, 1.07) 14.07
Judson(2003) 0.48 (0.12, 1.90) 9.74
Kolostova(2015) 2.19 (0.91, 5.29) 12.25
Obermayr(2013) 2.33 (0.28, 19.45) 6.65
Pearl(2014) 18.86 (5.01, 71.05) 10.02
Sang(2014) 3.60 (0.70, 18.54) 8.55
Overall (I-squared = 75.4%, p = 0.000) 2.18 (1.05, 4.54) 100.00
NOTE: Weights are from random effects analysis
.00427
1
234
C
study
OR (95% CI)
%
Weight
Banys(2009) 1.01 (0.40, 2.54) 8.30
Braun(2001) 2.70 (1.15, 6.33) 5.92
Fan(2009) 2.97 (0.13, 65.41) 0.54
Fehm(2006) 1.70 (0.61, 4.74) 5.14
Fehm(2013) 1.06 (0.70, 1.59) 40.84
Judson(2003) 0.73 (0.16, 3.38) 3.37
Kolostova(2015) 2.06 (0.72, 5.89) 4.34
Liu(2013) 1.67 (0.20, 13.98) 1.18
Obermayr(2013) 1.36 (0.65, 2.85) 11.53
Pearl(2014) 3.56 (0.74, 17.14) 1.19
Poveda(2011) 1.01 (0.47, 2.16) 12.13
Sang(2014) 1.50 (0.54, 4.19) 5.51
Overall (I-squared = 0.0%, p = 0.710) 1.32 (1.03, 1.69) 100.00
.0153
1
65.4

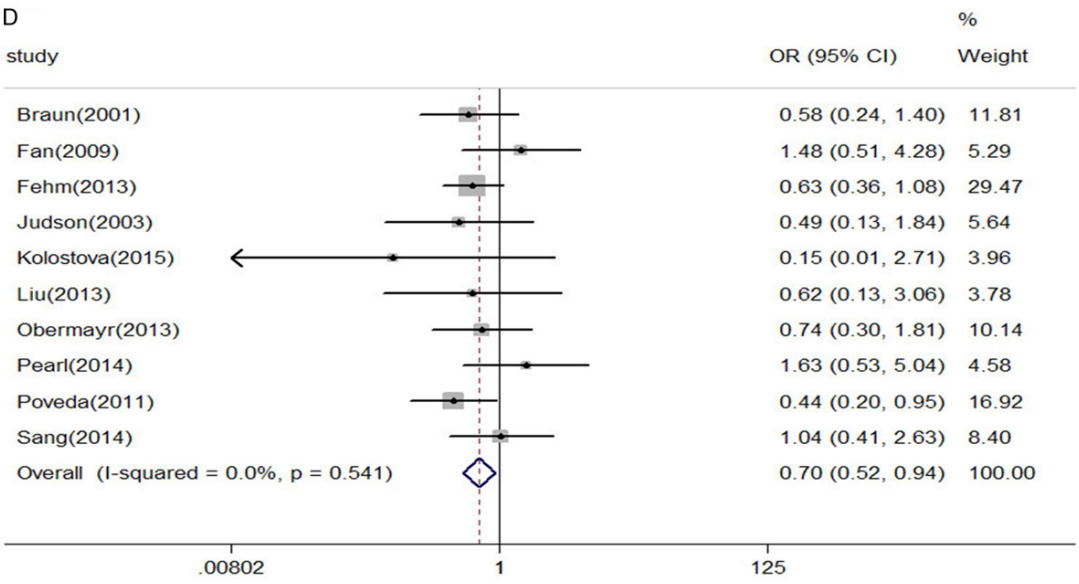


Figure 2. Forest plot of correlation between CTCs/DTCs and clinicopathological parameters. A. CA125 (high-expression vs low-expression). B. FIGO stage (III+IV vs I+II). C. Tumor grade (G3 vs G1G2). D. Cancer type (serous vs non-serous).

DTCs in high CA125 expression group than in low CA125 expression group (OR = 2.43 (1.44-4.09), Z = 3.34, P = 0.001). Heterogeneity among studies was not statistically significant (Q = 5.93, P = 0.313, fixed-effect).

Ten studies were analyzed for determining the correlation of CTCs/DTCs with FIGO stage (III+IV VS I+II) (**Figure 2B**) [10, 21, 27-31, 34-36]. The estimated pooled OR was 2.18 (1.05-4.54), indicating that the presence of CTCs/DTCs was associated with FIGO stage (Z = 2.08, P = 0.038). Heterogeneity among studies was of statistical significance (Q = 36.53, P < 0.001, random-effect).

Twelve studies were analyzed for examining the association of CTCs/DTCs with tumor grade (G3 VS G1G2) (**Figure 2C**) [10, 21, 22, 27-31, 33-36]. The estimated pooled OR was 1.32 (1.03-1.69), revealing that the presence of CTCs/DTCs was linked with tumor grade (Z = 2.18, P = 0.029). Heterogeneity among studies showed no statistical significance (Q = 8.04, P = 0.710, fixed-effect).

Ten studies were analyzed so as to study the relationship between CTCs/DTCs and cancer type (**Figure 2D**) [10, 22, 27, 28, 30, 31, 33-36]. The results demonstrated that compared with non-serous group, serous group was associated with a higher incidence of CTCs/DTCs (OR = 0.70 (0.52-0.94), Z = 2.39, P = 0.017). Heterogeneity among studies was not statistically significant (Q = 7.93, P = 0.541, fixed-effect).

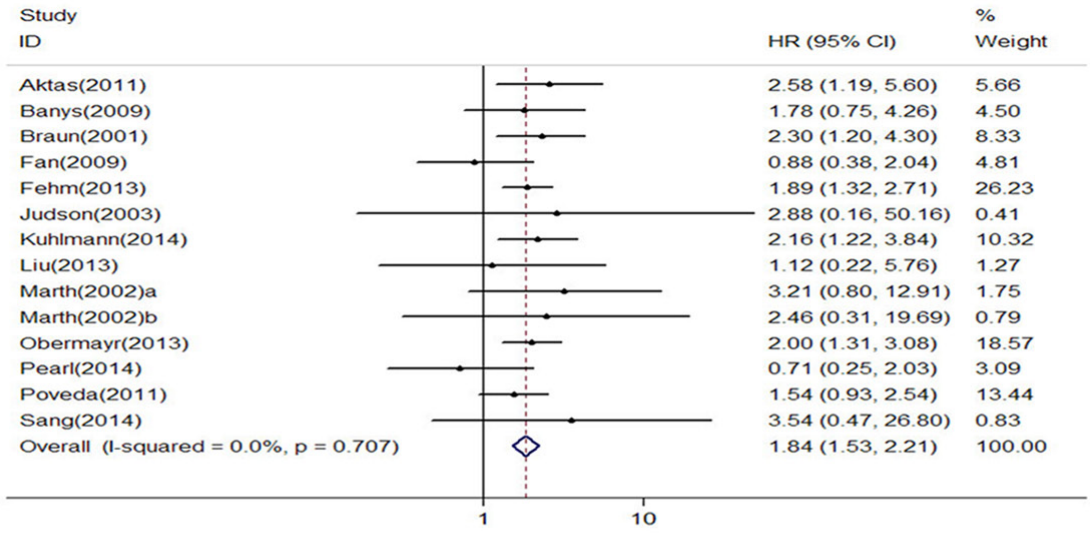
A higher incidence of CTCs/DTCs could not be observed in the lymph node metastasis group relative to non-lymph node metastasis group (OR = 1.64 (0.96-2.81), Z = 1.81, P = 0.070) [29, 31, 34, 36]. Heterogeneity among studies displayed no statistical significance (Q = 1.21, P = 0.750, fixed-effect).

Four studies were analyzed to examine the correlation of CTCs/DTCs with nodal status (N1 VS N0) [21, 27-29]. An estimated pooled OR of 0.70 (0.51-0.98) was obtained, suggesting association of the presence of CTCs/DTCs with nodal status (Z = 2.11, P = 0.035). Heterogeneity among studies was not statistically significant (Q = 3.13, P = 0.371, fixed-effect).

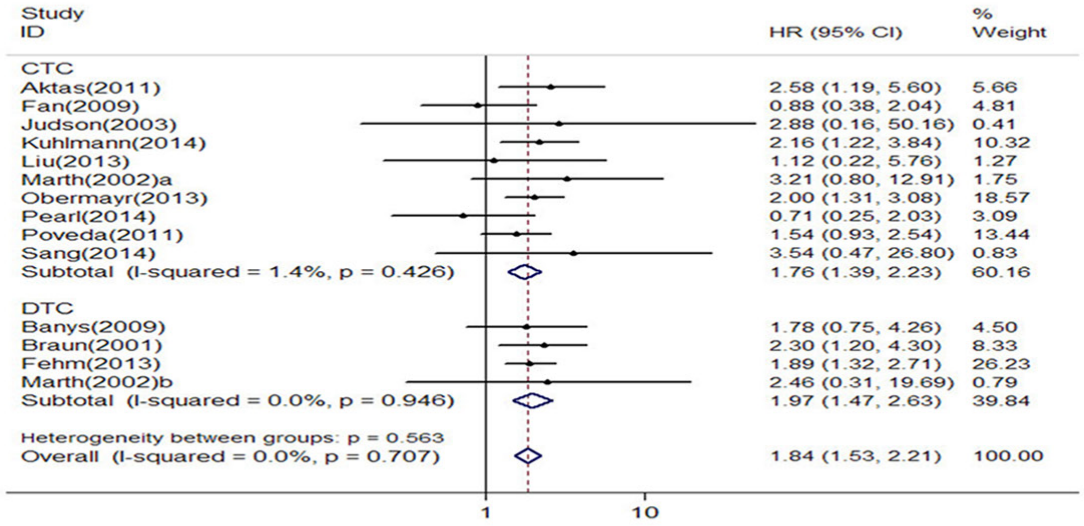
Compared with platinum-sensitive group, platinum-resistant group had a higher incidence of CTCs/DTCs (OR = 2.05 (1.03-4.07), Z = 2.04, P = 0.041) [22, 35]. Heterogeneity among studies displayed no statistical significance (Q = 0.55, P = 0.460, fixed-effect).

Two studies were analyzed to investigate the relationship between CTCs/DTCs and resection

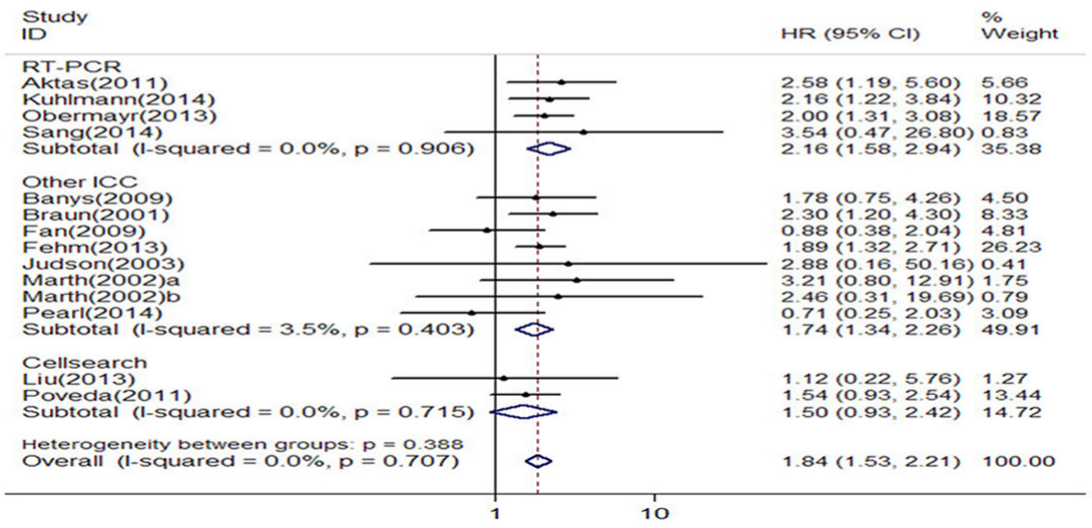
A


Study ID
HR (95% CI)
% Weight
Aktas(2011) 2.58 (1.19, 5.60) 5.66
Banys(2009) 1.78 (0.75, 4.26) 4.50
Braun(2001) 2.30 (1.20, 4.30) 8.33
Fan(2009) 0.88 (0.38, 2.04) 4.81
Fehm(2013) 1.89 (1.32, 2.71) 26.23
Judson(2003) 2.88 (0.16, 50.16) 0.41
Kuhlmann(2014) 2.16 (1.22, 3.84) 10.32
Liu(2013) 1.12 (0.22, 5.76) 1.27
Marth(2002)a 3.21 (0.80, 12.91) 1.75
Marth(2002)b 2.46 (0.31, 19.69) 0.79
Obermayr(2013) 2.00 (1.31, 3.08) 18.57
Pearl(2014) 0.71 (0.25, 2.03) 3.09
Poveda(2011) 1.54 (0.93, 2.54) 13.44
Sang(2014) 3.54 (0.47, 26.80) 0.83
Overall (I-squared = 0.0%, p = 0.707) 1.84 (1.53, 2.21) 100.00
1
10

B


Study ID
HR (95% CI)
% Weight
CTC
Aktas(2011) 2.58 (1.19, 5.60) 5.66
Fan(2009) 0.88 (0.38, 2.04) 4.81
Judson(2003) 2.88 (0.16, 50.16) 0.41
Kuhlmann(2014) 2.16 (1.22, 3.84) 10.32
Liu(2013) 1.12 (0.22, 5.76) 1.27
Marth(2002)a 3.21 (0.80, 12.91) 1.75
Obermayr(2013) 2.00 (1.31, 3.08) 18.57
Pearl(2014) 0.71 (0.25, 2.03) 3.09
Poveda(2011) 1.54 (0.93, 2.54) 13.44
Sang(2014) 3.54 (0.47, 26.80) 0.83
Subtotal (I-squared = 1.4%, p = 0.426) 1.76 (1.39, 2.23) 60.16
DTC
Banys(2009) 1.78 (0.75, 4.26) 4.50
Braun(2001) 2.30 (1.20, 4.30) 8.33
Fehm(2013) 1.89 (1.32, 2.71) 26.23
Marth(2002)b 2.46 (0.31, 19.69) 0.79
Subtotal (I-squared = 0.0%, p = 0.946) 1.97 (1.47, 2.63) 39.84
Heterogeneity between groups: p = 0.563
Overall (I-squared = 0.0%, p = 0.707) 1.84 (1.53, 2.21) 100.00
1
10

C


Study ID
HR (95% CI)
% Weight
RT-PCR
Aktas(2011) 2.58 (1.19, 5.60) 5.66
Kuhlmann(2014) 2.16 (1.22, 3.84) 10.32
Obermayr(2013) 2.00 (1.31, 3.08) 18.57
Sang(2014) 3.54 (0.47, 26.80) 0.83
Subtotal (I-squared = 0.0%, p = 0.906) 2.16 (1.58, 2.94) 35.38
Other ICC
Banys(2009) 1.78 (0.75, 4.26) 4.50
Braun(2001) 2.30 (1.20, 4.30) 8.33
Fan(2009) 0.88 (0.38, 2.04) 4.81
Fehm(2013) 1.89 (1.32, 2.71) 26.23
Judson(2003) 2.88 (0.16, 50.16) 0.41
Marth(2002)a 3.21 (0.80, 12.91) 1.75
Marth(2002)b 2.46 (0.31, 19.69) 0.79
Pearl(2014) 0.71 (0.25, 2.03) 3.09
Subtotal (I-squared = 3.5%, p = 0.403) 1.74 (1.34, 2.26) 49.91
Cellsearch
Liu(2013) 1.12 (0.22, 5.76) 1.27
Poveda(2011) 1.54 (0.93, 2.54) 13.44
Subtotal (I-squared = 0.0%, p = 0.715) 1.50 (0.93, 2.42) 14.72
Heterogeneity between groups: p = 0.388
Overall (I-squared = 0.0%, p = 0.707) 1.84 (1.53, 2.21) 100.00
1
10

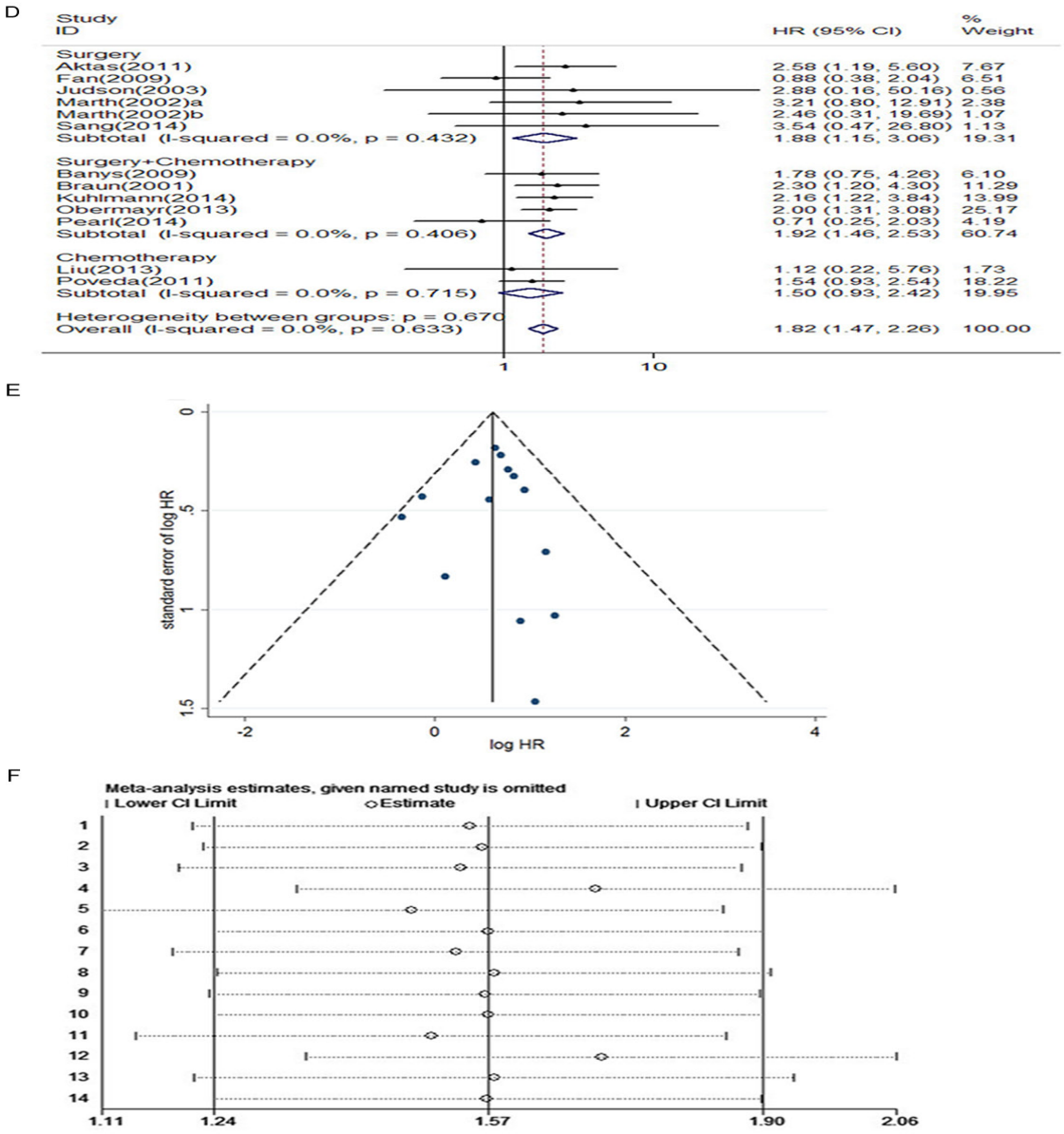


Figure 3. The meta-analysis of hazard ratio estimates for OS in ovarian cancer. OS = overall survival. A. Forest plot showing the meta-analysis of hazard ratio estimates for OS in overall patients. B. Subgroup analysis based on different Samples. C. Subgroup analysis based on different detection methods. D. Subgroup analysis based on different treatment methods. E. Funnel plot for the pooled HRs in OS. F. Sensitivity analysis for the pooled HRs in OS.

status (R1-2 VS R0), the results of which indicated that the incidence of CTCs/DTCs was not associated with resection status (0.97 (0.66-1.41), Z = 0.17, P = 0.865) [21, 28]. Heterogeneity among studies was not statistically significant (Q = 0.57, p = 0.450, fixed-effect).

Two studies were analyzed to illustrate the association of CTCs/DTCs with tumor size (T2-4 VS T1), the results of which suggested that the incidence of CTCs/DTCs was not associated with resection status (1.06 (0.22-5.20), Z = 0.07, P = 0.945) [21, 22]. Heterogeneity among studies was of no statistical significance (Q = 3.49, p = 0.062, random-effect).

Four studies were analyzed for clarifying the relationship between CTCs/DTCs and ascites [22, 27, 31, 34]. Compared with non-ascites group, higher incidence of CTCs/DTCs was

observed in ascites group (OR = 2.16 (1.43-3.27), Z = 3.66, P = 0.000). Heterogeneity among studies displayed no statistical significance (Q = 2.43, P = 0.487, fixed-effect).

Three studies were analyzed to explain the correlation of CTCs/DTCs with debulking (Optimal VS Suboptimal), the results of which revealed no association of the incidence of CTCs/DTCs with debulking (OR = 0.99 (0.45-2.22), Z = 0.02, P = 0.986) [10, 22, 36]. Heterogeneity among studies displayed no statistical significance (Q = 2.34, p = 0.310, fixed-effect).

To determine the relevance of CTCs/DTCs with race (White VS non-white), two studies were analyzed, the results of which indicated that the incidence of CTCs/DTCs was not associated with race. (OR = 1.44 (0.27-7.73), Z = 0.43, P = 0.668) [10, 22]. Heterogeneity among studies was not statistically significant (Q = 0.89, P = 0.347, fixed-effect).

OS and CTCs/DTCs

Effect of CTCs/DTCs on overall survival (OS) of ovarian cancer

HRs for OS were analyzed in 13 studies including 1812 patients with ovarian cancer. 3 studies were excluded due to data deficiency regarding OS [26, 29, 31]. Five of the 13 studies confirmed the correlation of the presence of CTCs/DTCs with OS [25, 27, 28, 32, 34]; while the remaining 8 indicated no correlation of CTCs/DTCs with OS [10, 20-22, 30, 33, 35, 36]. Estimated pooled HR was calculated adopting a fixed effect model since the heterogeneity among studies was greater than 0.05 (Q = 9.84, P = 0.707). The pooled HR showed that CTCs/DTCs were significantly associated with OS, demonstrating that CTCs/DTCs would increase the risk of overall mortality in ovarian cancer (HR = 1.84 (1.53-2.21), Z = 6.48, P < 0.001) (**Figure 3A**).

Subgroup analyses

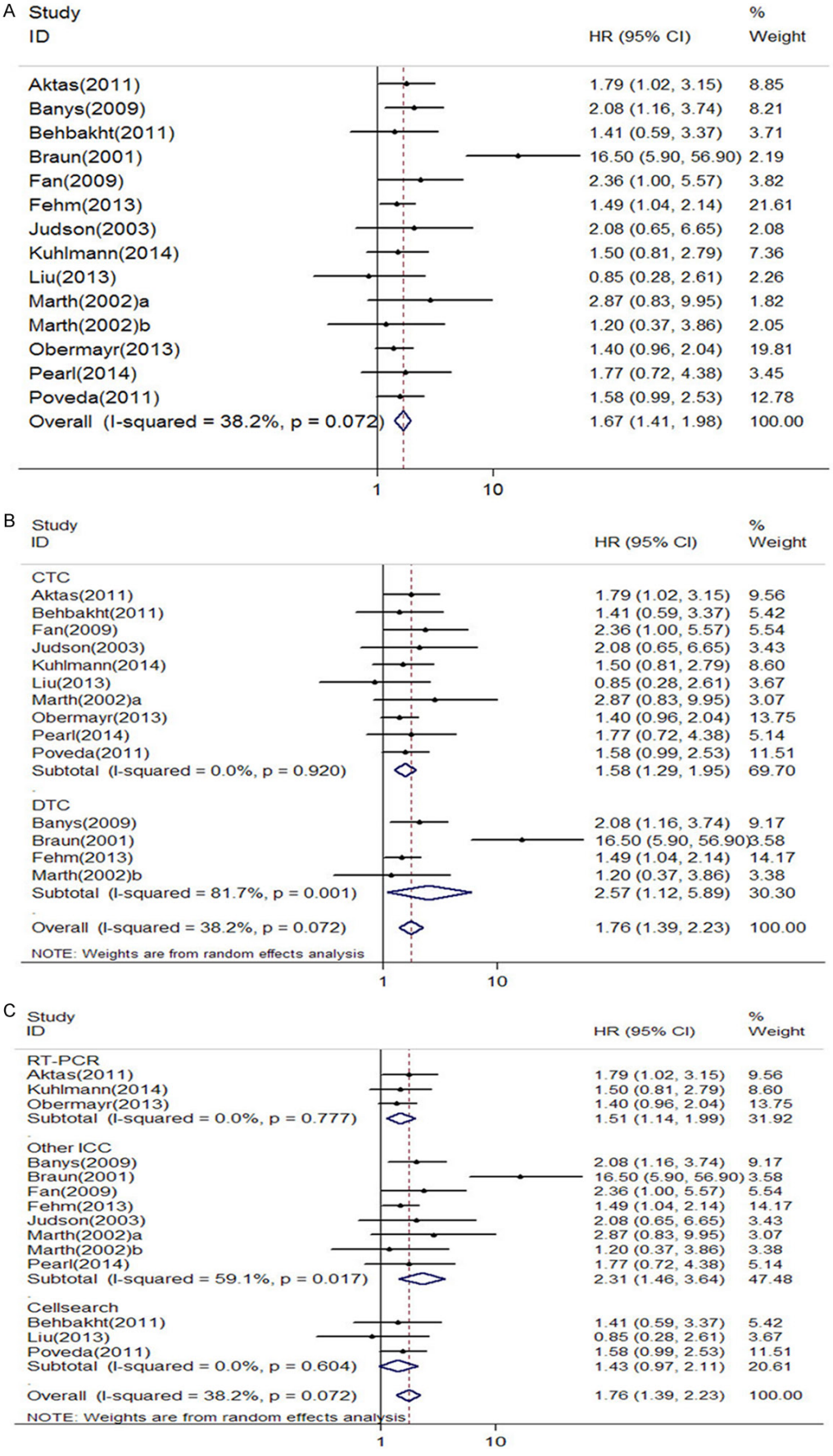
Sampling types: The association of OS with CTCs from peripheral blood (PB) [10, 20, 22, 25, 30, 32-36] and DTCs from bone marrow (BM) [20, 21, 27, 28] was detected, respectively. The enrolled studies were classified into CTCs group and DTCs group for sub-group analyses. The results showed that both CTCs and DTCs were markedly associated with OS (HR = 1.76, 95% CI (1.39-2.23), Z = 4.66, P < 0.001 and HR = 1.97, 95% CI (1.47-2.63), Z = 4.54, P < 0.001, respectively; **Figure 3B**). It was revealed in 3 out of the 10 studies concerning PB that CTCs were associated with increased risk of death [25, 32, 34]. 2 of the 4 studies regarding BM illustrated a remarkable prognostic value for OS [27, 28]. There were no demonstrated heterogeneity in PB group and BM group.

Detection methods: CTCs/DTCs were detected by RT-PCR technology in 4 studies [25, 32, 34, 36], by CellSearch system in 2 studies [22, 33], as well as by other ICC methods in 7 studies [10, 20, 21, 27, 28, 30, 35]. Notable prognostic value of CTCs/DTCs for OS could be seen in the "RT-PCR" subgroup (HR = 2.16; 95% CI (1.58-2.94), P < 0.001) and the "other ICC" subgroup (HR = 1.74; 95% CI (1.34-2.26), P < 0.001), which could not be observed in the "CellSearch" subgroup (HR = 1.50; 95% CI (0.93-2.42), P = 0.099; **Figure 3C**). Statistical heterogeneity was not found in "RT-PCR" subgroup, "CellSearch" subgroup or "other ICC" subgroup (I^2 = 3.5%, P = 0.403; I^2 = 0.0%, P = 0.715 and I^2 = 0.0%, P = 0.906, respectively). The results indicated that detection methods of both RT-PCR and other ICC were able to detect CTCs/DTCs in predicting prognosis for patients.

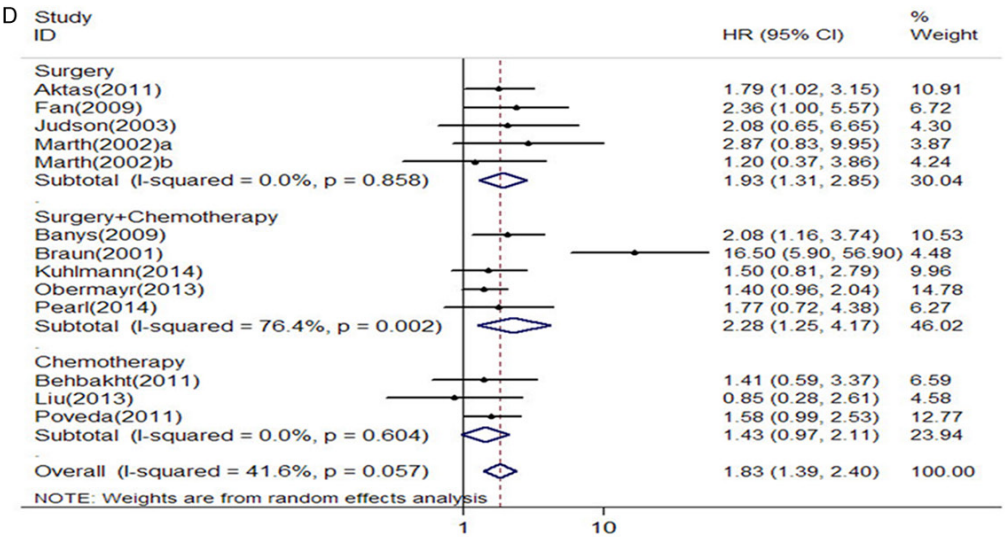
Treatment methods: As was shown in the subgroup analyses based on treatment methods, patients received surgery alone in five studies [10, 20, 25, 30, 36], chemotherapy alone in two studies [22, 33], and surgery combined with chemotherapy in the other five studies [21, 27, 32, 34, 35]. The results showed that "Surgery" subgroup (HR = 1.88; 95% CI (1.15-3.06), P = 0.011) and the "Surgery combined with Chemotherapy" subgroup (HR = 1.92; 95% CI (1.46-2.53), P < 0.001) were associated with notable prognostic value of CTCs/DTCs for OS, while that was not significant in the "Chemotherapy" subgroup (HR = 1.50; 95% CI (0.93-2.42), P = 0.099; **Figure 3D**).

Meta-regression analyses

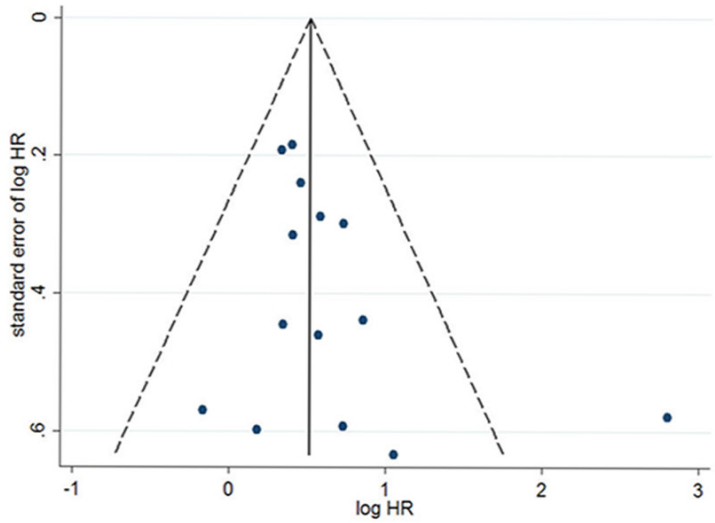
Meta-regression was performed using the following covariates: sample size, publication year, detection method and treatment method.


A
Study ID
HR (95% CI)
% Weight
Aktas(2011) 1.79 (1.02, 3.15) 8.85
Banys(2009) 2.08 (1.16, 3.74) 8.21
Behbakht(2011) 1.41 (0.59, 3.37) 3.71
Braun(2001) 16.50 (5.90, 56.90) 2.19
Fan(2009) 2.36 (1.00, 5.57) 3.82
Fehm(2013) 1.49 (1.04, 2.14) 21.61
Judson(2003) 2.08 (0.65, 6.65) 2.08
Kuhlmann(2014) 1.50 (0.81, 2.79) 7.36
Liu(2013) 0.85 (0.28, 2.61) 2.26
Marth(2002)a 2.87 (0.83, 9.95) 1.82
Marth(2002)b 1.20 (0.37, 3.86) 2.05
Obermayr(2013) 1.40 (0.96, 2.04) 19.81
Pearl(2014) 1.77 (0.72, 4.38) 3.45
Poveda(2011) 1.58 (0.99, 2.53) 12.78
Overall (I-squared = 38.2%, p = 0.072) 1.67 (1.41, 1.98) 100.00
1
10
B
Study ID
HR (95% CI)
% Weight
CTC
Aktas(2011) 1.79 (1.02, 3.15) 9.56
Behbakht(2011) 1.41 (0.59, 3.37) 5.42
Fan(2009) 2.36 (1.00, 5.57) 5.54
Judson(2003) 2.08 (0.65, 6.65) 3.43
Kuhlmann(2014) 1.50 (0.81, 2.79) 8.60
Liu(2013) 0.85 (0.28, 2.61) 3.67
Marth(2002)a 2.87 (0.83, 9.95) 3.07
Obermayr(2013) 1.40 (0.96, 2.04) 13.75
Pearl(2014) 1.77 (0.72, 4.38) 5.14
Poveda(2011) 1.58 (0.99, 2.53) 11.51
Subtotal (I-squared = 0.0%, p = 0.920) 1.58 (1.29, 1.95) 69.70
DTC
Banys(2009) 2.08 (1.16, 3.74) 9.17
Braun(2001) 16.50 (5.90, 56.90) 3.58
Fehm(2013) 1.49 (1.04, 2.14) 14.17
Marth(2002)b 1.20 (0.37, 3.86) 3.38
Subtotal (I-squared = 81.7%, p = 0.001) 2.57 (1.12, 5.89) 30.30
Overall (I-squared = 38.2%, p = 0.072) 1.76 (1.39, 2.23) 100.00
NOTE: Weights are from random effects analysis
1
10
C
Study ID
HR (95% CI)
% Weight
RT-PCR
Aktas(2011) 1.79 (1.02, 3.15) 9.56
Kuhlmann(2014) 1.50 (0.81, 2.79) 8.60
Obermayr(2013) 1.40 (0.96, 2.04) 13.75
Subtotal (I-squared = 0.0%, p = 0.777) 1.51 (1.14, 1.99) 31.92
Other ICC
Banys(2009) 2.08 (1.16, 3.74) 9.17
Braun(2001) 16.50 (5.90, 56.90) 3.58
Fan(2009) 2.36 (1.00, 5.57) 5.54
Fehm(2013) 1.49 (1.04, 2.14) 14.17
Judson(2003) 2.08 (0.65, 6.65) 3.43
Marth(2002)a 2.87 (0.83, 9.95) 3.07
Marth(2002)b 1.20 (0.37, 3.86) 3.38
Pearl(2014) 1.77 (0.72, 4.38) 5.14
Subtotal (I-squared = 59.1%, p = 0.017) 2.31 (1.46, 3.64) 47.48
Cellsearch
Behbakht(2011) 1.41 (0.59, 3.37) 5.42
Liu(2013) 0.85 (0.28, 2.61) 3.67
Poveda(2011) 1.58 (0.99, 2.53) 11.51
Subtotal (I-squared = 0.0%, p = 0.604) 1.43 (0.97, 2.11) 20.61
Overall (I-squared = 38.2%, p = 0.072) 1.76 (1.39, 2.23) 100.00
NOTE: Weights are from random effects analysis
1
10

D


Study ID
HR (95% CI)
% Weight
Surgery
Aktas(2011) 1.79 (1.02, 3.15) 10.91
Fan(2009) 2.36 (1.00, 5.57) 6.72
Judson(2003) 2.08 (0.65, 6.65) 4.30
Marth(2002)a 2.87 (0.83, 9.95) 3.87
Marth(2002)b 1.20 (0.37, 3.86) 4.24
Subtotal (I-squared = 0.0%, p = 0.858) 1.93 (1.31, 2.85) 30.04
Surgery+Chemotherapy
Banys(2009) 2.08 (1.16, 3.74) 10.53
Braun(2001) 16.50 (5.90, 56.90) 4.48
Kuhlmann(2014) 1.50 (0.81, 2.79) 9.96
Obermayr(2013) 1.40 (0.96, 2.04) 14.78
Pearl(2014) 1.77 (0.72, 4.38) 6.27
Subtotal (I-squared = 76.4%, p = 0.002) 2.28 (1.25, 4.17) 46.02
Chemotherapy
Behbakht(2011) 1.41 (0.59, 3.37) 6.59
Liu(2013) 0.85 (0.28, 2.61) 4.58
Poveda(2011) 1.58 (0.99, 2.53) 12.77
Subtotal (I-squared = 0.0%, p = 0.604) 1.43 (0.97, 2.11) 23.94
Overall (I-squared = 41.6%, p = 0.057) 1.83 (1.39, 2.40) 100.00
NOTE: Weights are from random effects analysis
1
10

E


standard error of log HR
0
.2
.4
.6
-1
0
1
2
3
log HR

F

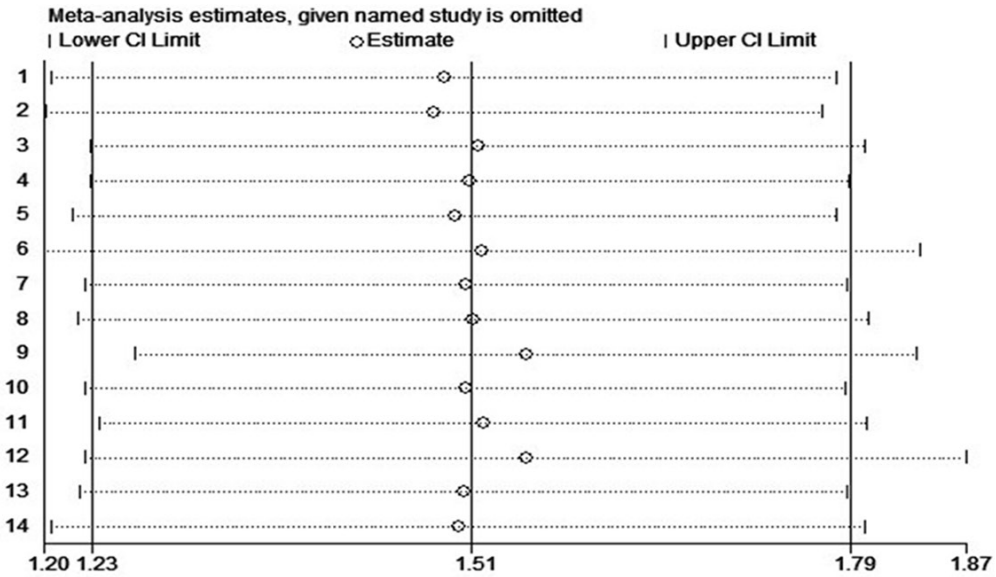

Meta-analysis estimates, given named study is omitted
Lower CI Limit
Estimate
Upper CI Limit
1
2
3
4
5
6
7
8
9
10
11
12
13
14
1.20 1.23
1.51
1.79
1.87

Figure 4. The meta-analysis of hazard ratio estimates for PFS/DFS in ovarian cancer. PFS = Progress-free survival, DFS = Disease-Free Survival. A. Forest plot showing the meta-analysis of hazard ratio estimates for PFS/DFS in overall patients. B. Subgroup analysis based on different Samples. C. Subgroup analysis based on different detection methods. D. Subgroup analysis based on different treatment methods. E. Funnel plot for the pooled HRs in PFS/DFS. F. Sensitivity analysis for the pooled HRs in PFS/DFS.

It was shown in a multivariate analysis that the explanatory variables influencing the estimated HRs for OS were publication year (coefficient = -0.092, standard error = 0.038, p = 0.043) and treatment method (coefficient = -0.489, standard error = 0.190, p = 0.033), while no significant association could be observed in sample size (p = 0.811) or detection method (p = 0.830).

Publication bias

Publication bias was assessed using Egger's test and Begg's test. There was no evidence of asymmetry (P = 0.891; P = 0.870) in a pooled analysis of studies on OS (**Figure 3E**). No publication bias was seen in all subsequent subgroup analyses, revealing no publication bias and reliable results of the study.

Sensitivity analysis

A sensitivity analysis was performed by estimating the average HR in the absence of each study, the results of which indicated that no single study dominated our results (**Figure 3F**).

Progression-free survival (PFS)/disease-free survival (DFS) and CTCs/DTCs

Effect of CTCs/DTCs on PFS/DFS in ovarian cancer

HRs for PFS/DFS were analyzed in 13 studies involving 1775 patients with ovarian cancer. 3 studies were excluded for data deficiency regarding PFS/DFS [29, 31, 36]. 5 out of the 13 studies confirmed the correlation of the presence of CTCs/DTCs with PFS/DFS [10, 21, 25, 27, 28]. Conversely, the remaining 8 studies suggested no relationship between them [20, 22, 26, 30, 32-35]. A fixed effect model was applied to calculate the estimated pooled HR since heterogeneity among studies was greater than 0.05 (Q = 21.05, p = 0.072). The pooled HR of all studies indicated that CTCs/DTCs were significantly associated with PFS/DFS (HR = 1.67 (1.41-1.98), Z = 6.01, P < 0.001), demonstrating that higher CTCs/DTCs level would increase risk of disease progression in ovarian cancer (**Figure 4A**).

Subgroup analyses

Sampling types: The association of PFS/DFS with CTCs from peripheral blood (PB) [10, 20, 22, 25, 26, 30, 32-35] and DTCs from bone marrow (BM) [20, 21, 27, 28] was detected, respectively. The enrolled studies were classified into CTCs group and DTCs group for subgroup analysis. Results of the meta-analysis showed that patients with detected CTCs in PB group and DTCs in BM group had shorter PFS/DFS (HR = 1.58 (1.29-1.95), Z = 4.35, P < 0.001 and HR = 2.57 (1.12-5.89), Z = 2.23, P = 0.026, respectively; **Figure 4B**). 2 of the 10 studies concerning PB illustrated that the presence of CTCs was associated with disease progression [10, 25]. 3 out of the 4 studies about BM suggested a marked prognostic value for PFS/DFS [21, 27, 28]. There was no demonstrated heterogeneity in PB group or BM group.

Detection methods: CTCs/DTCs were detected by RT-PCR technology in 3 studies [25, 32, 34], by CellSearch system in 3 studies [22, 26, 33], and by other ICC methods in 7 studies [10, 20, 21, 27, 28, 30, 35]. A distinct prognostic value of CTCs/DTCs for PFS/DFS could be observed in the "RT-PCR" subgroup (HR = 1.51; 95% CI (1.14-1.99), P = 0.004) and the "other ICC" subgroup (HR = 2.31; 95% CI (1.46-3.64), P < 0.001), which could not be observed in the "CellSearch" subgroup (HR = 1.43; 95% CI (0.97-2.11), P = 0.068; **Figure 4C**). Statistical heterogeneity was not found in "RT-PCR" subgroup and "CellSearch" subgroup (I^2 = 0.0%, P = 0.777; I^2 = 0.0%, P = 0.604; respectively), but in "other ICC" subgroup (I^2 = 59.1%, P = 0.017). The results indicated that detection methods of both RT-PCR and other ICC were able to detect CTCs/DTCs in predicting prognosis for patients.

Treatment methods: As was shown in the subgroup analyses based on treatment methods, patients received surgery alone in four studies [10, 20, 25, 30], chemotherapy alone in three studies [22, 26, 33], and surgery combined with chemotherapy in the other five studies [21, 27, 32, 34, 35]. The results showed that "Surgery" subgroup (HR = 1.93; 95% CI (1.31-

2.85), P = 0.001) and the "Surgery combined with Chemotherapy" subgroup (HR = 2.28; 95% CI (1.25-4.17), P = 0.007) were associated with apparent prognostic value of CTCs/DTCs for PFS/DFS, while that was not significant in the "Chemotherapy" subgroup (HR = 1.43; 95% CI (0.97-2.11), P = 0.068; **Figure 4D**).

Meta-regression analyses

Meta-regression was carried out using the following covariates: sample size, publication year, tumor stage, detection method, and treatment method. As was shown in a multivariate analysis, no significant association could be observed in sample size (p = 0.760), publication year (p = 0.095), tumor stage (p = 0.395), detection method (p = 0.457), or treatment method (p = 0.371).

Publication bias

Publication bias was evaluated by Egger's test and Begg's test. There was no evidence of asymmetry (P = 0.155; P = 0.208) in a pooled analysis of studies on PFS/DFS (**Figure 4E**). No publication bias was seen in all subsequent subgroup analyses, indicating no publication bias and reliable results of the study.

Sensitivity analysis

A sensitivity analysis was performed by estimating the average HR in the absence of each study, the results of which indicated that no single study dominated our results (**Figure 4F**).

Discussion

The present meta-analysis is carried out based on a large pool of clinical studies, which differs from the other 3 meta-analyses published in 2015 [37-39]. Both Zeng et al. and Zhou et al. suggested the predictive value of CTCs in ovarian cancer only, while Cui et al. considered the predictive values of both CTCs and DTCs in ovarian cancer. Correlation of CTCs/DTCs with clinicopathological parameters was analyzed from the points of view of cancer type, FIGO, lymph node metastasis, debulking and platinum sensitivity in research by Cui et al. In our research, more parameters are discussed, including CA125, grade, tumor size, ascites and race. As is indicated in our meta-analysis, CTCs/DTCs are significantly associated with CA125, FIGO, grade, cancer type, nodal status, platinum sensitivity and ascites, but not with lymph node metastasis, resection status, tumor size, debulking or race of ovarian cancer patients. Ovarian cancer mainly grows and recurs in abdominal cavity [40]. Lymph node metastasis occurs only when cancer cells invade lymphatic vessels while CTCs/DTCs occur only when cancer cells invade blood vessels [41]. Therefore CTCs/DTCs are not significantly associated with lymph node metastasis; furthermore, CTCs/DTCs are not correlated with tumor size or race. Some researchers believe that CTCs/DTCs are associated with resection status and debulking, which is different from our meta-analysis.

Patients in CTCs/DTCs-positive group have worse OS and PFS/DFS compared with those in CTCs/DTCs-negative group, as can be observed from available evidence, indicating that the presence of CTCs/DTCs is significantly associated with a poorer survival. In this meta-analysis, subgroup analyses are carried out from the following three aspects, namely, sampling type, detection method and treatment method. The results show that DTCs and CTCs can not only increase the risk of death in patients with ovarian cancer, but also contributes to assessing the prognosis of ovarian cancer. Both RT-PCR and other ICC detection methods are able to detect CTCs/DTCs in predicting prognosis for patients with ovarian cancer. It is also shown in subgroup analyses that the prognostic value of CTCs/DTCs for OS and PFS/DFS is significant in the "Surgery" subgroup (HR 1.88, P = 0.011; HR 1.93, P = 0.001) and the "Surgery combined with Chemotherapy" subgroup (HR 1.92, P < 0.001; HR 2.28, P = 0.007), but not in the "Chemotherapy" subgroup (HR 1.50, P = 0.099; HR 1.43, P = 0.068). However, it can hardly determine that whether treatment method would influence the prognostic value of CTCs/DTCs, which can be attributed to several aspects, namely, different time of CTCs/DTCs detection, operative type, chemotherapy regimen, treatment effect and so on. Consequently, more clinical studies are required to confirm such results.

It is indicated in this meta-analysis that CTCs/DTCs are significantly linked with a poor survival outcome. However, this meta-analysis is

inevitably associated with some limitations. Firstly, although studies are retrieved without the limitation of time and language, unpublished data are not searched. Secondly, sample size in each study is relatively small, the results of which should be confirmed by prospective clinical studies with larger sample size. Thirdly, the enrolled studies vary in the definition of presence of CTCs/DTCs and detection method; besides, no uniform standard is available for the definition of positive CTCs/DTCs results. Validation studies are still lacking, so an international standard of the definition of "positive CTCs/DTCs" is necessary.

In conclusion, detection of CTCs/DTCs in ovarian cancer patients shows a significant prognostic value, which may be treated as a reliable non-invasive prognostic marker for ovarian cancer and can be served as a tool to guide treatment in cancer patients in the future. CTCs/DTCs can significantly predict advanced tumor stage and treatment response, but not lymph node metastasis in patients, FIGO or tumor size of ovarian cancer. Moreover, CTCs/DTCs are also significantly associated with a poorer survival rate.

Acknowledgements

This study was funded by The National Natural Science Foundation of China (grant number 81370703).

Disclosure of conflict of interest

None.

Address correspondence to: Xiaocheng Wang, Department of Medical Record & Statistics, Shanxi Provincial People's Hospital, Taiyuan 030012, Shanxi Province, China. Tel: (+86) 0351-4960114; E-mail: buyi21shiji@163.com

References

[1] Jacobs IJ, Menon U, Ryan A, Gentry-Maharaj A, Burnell M, Kalsi JK, Amso NN, Apostolidou S, Benjamin E, Cruickshank D, Crump DN, Davies SK, Dawnay A, Dobbs S, Fletcher G, Ford J, Godfrey K, Gunu R, Habib M, Hallett R, Herod J, Jenkins H, Karpinskyj C, Leeson S, Lewis SJ, Liston WR, Lopes A, Mould T, Murdoch J, Oram D, Rabideau DJ, Reynolds K, Scott I, Seif MW, Sharma A, Singh N, Taylor J, Warburton F, Widschwendter M, Williamson K, Woolas R, Fallowfield L, McGuire AJ, Campbell S, Parmar M and Skates SJ. Ovarian cancer screening and mortality in the UK collaborative trial of ovarian Cancer Screening (UKCTOCS): a randomised controlled trial. Lancet 2016; 387: 945-956.

[2] Jelovac D and Armstrong DK. Recent progress in the diagnosis and treatment of ovarian cancer. CA Cancer J Clin 2011; 61: 183-203.

[3] Urban RR, He H, Alfonso R, Hardesty MM, Gray HJ and Goff BA. Ovarian cancer outcomes: Predictors of early death. Gynecol Oncol 2016; 140: 474-480.

[4] Jacobs IJ and Menon U. Progress and challenges in screening for early detection of ovarian cancer. Mol Cell Proteomics 2004; 3: 355-366.

[5] Jemal A, Tiwari RC, Murray T, Ghafoor A, Samuels A, Ward E, Feuer EJ and Thun MJ. Cancer statistics, 2004. CA Cancer J Clin 2004; 54: 8-29.

[6] La Vecchia C. Ovarian cancer: epidemiology and risk factors. Eur J Cancer Prev 2017; 26: 55-62.

[7] Bast RC Jr. Status of tumor markers in ovarian cancer screening. J Clin Oncol 2003; 21 Suppl: 200s-205s.

[8] Jacobs I and Bast RC Jr. The CA 125 tumour-associated antigen: a review of the literature. Hum Reprod 1989; 4: 1-12.

[9] Zhang P, Wang C, Cheng L, Zhang P, Guo L, Liu W, Zhang Z, Huang Y, Ou Q, Wen X and Tian Y. Comparison of HE4, CA125, and ROMA diagnostic accuracy: a prospective and multicenter study for Chinese women with epithelial ovarian cancer. Medicine (Baltimore) 2015; 94: e2402.

[10] Fan T, Zhao Q, Chen JJ, Chen WT and Pearl ML. Clinical significance of circulating tumor cells detected by an invasion assay in peripheral blood of patients with ovarian cancer. Gynecol Oncol 2009; 112: 185-191.

[11] Lianidou ES, Strati A and Markou A. Circulating tumor cells as promising novel biomarkers in solid cancers. Crit Rev Clin Lab Sci 2014; 51: 160-171.

[12] Yap TA, Lorente D, Omlin A, Olmos D and de Bono JS. Circulating tumor cells: a multifunctional biomarker. Clin Cancer Res 2014; 20: 2553-2568.

[13] Braun S and Pantel K. [Diagnosis and clinical significance of disseminated tumor cells in bone marrow]. Dtsch Med Wochenschr 2000; 125: 1237-1239.

[14] Pantel K and Alix-Panabières C. Bone marrow as a reservoir for disseminated tumor cells: a special source for liquid biopsy in cancer patients. Bonekey Rep 2014; 3: 584.

[15] Gonzalez-Angulo AM, Morales-Vasquez F and Hortobagyi GN. Overview of resistance to sys-

temic therapy in patients with breast cancer. Adv Exp Med Biol 2007; 608: 1-22.
[16] Huang X, Gao P, Song Y, Sun J, Chen X, Zhao J, Xu H and Wang Z. Meta-analysis of the prognostic value of circulating tumor cells detected with the cellsearch system in colorectal cancer. BMC Cancer 2015; 15: 202.
[17] Magnowski P, Bochynski H, Nowak-Markwitz E, Zabel M and Spaczynski M. [Circulating tumor cells (CTCs)--clinical significance in patients with ovarian cancer]. Ginekol Pol 2012; 83: 291-294.
[18] Maltoni R, Fici P, Amadori D, Gallerani G, Cocchi C, Zoli M, Rocca A, Cecconetto L, Folli S, Scarpi E, Serra P and Fabbri F. Circulating tumor cells in early breast cancer: a connection with vascular invasion. Cancer Lett 2015; 367: 43-48.
[19] Romero-Laorden N, Olmos D, Fehm T, Garcia-Donas J and Diaz-Padilla I. Circulating and disseminated tumor cells in ovarian cancer: a systematic review. Gynecol Oncol 2014; 133: 632-639.
[20] Marth C, Kisic J, Kaern J, Tropé C and Fodstad Ø. Circulating tumor cells in the peripheral blood and bone marrow of patients with ovarian carcinoma do not predict prognosis. Cancer 2002; 94: 707-712.
[21] Banys M, Solomayer EF, Becker S, Krawczyk N, Gardanis K, Staebler A, Neubauer H, Wallwiener D and Fehm T. Disseminated tumor cells in bone marrow may affect prognosis of patients with gynecologic malignancies. Int J Gynecol Cancer 2009; 19: 948-952.
[22] Poveda A, Kaye SB, McCormack R, Wang S, Parekh T, Ricci D, Lebedinsky CA, Tercero JC, Zintl P and Monk BJ. Circulating tumor cells predict progression free survival and overall survival in patients with relapsed/recurrent advanced ovarian cancer. Gynecol Oncol 2011; 122: 567-572.
[23] Tierney JF, Stewart LA, Ghersi D, Burdett S and Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. Trials 2007; 8: 16.
[24] Higgins JP, Thompson SG, Deeks JJ and Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003; 327: 557-560.
[25] Aktas B, Kasimir-Bauer S, Heubner M, Kimmig R and Wimberger P. Molecular profiling and prognostic relevance of circulating tumor cells in the blood of ovarian cancer patients at primary diagnosis and after platinum-based chemotherapy. Int J Gynecol Cancer 2011; 21: 822-830.
[26] Behbakht K, Sill MW, Darcy KM, Rubin SC, Mannel RS, Waggoner S, Schilder RJ, Cai KQ, Godwin AK and Alpaugh RK. Phase II trial of the mTOR inhibitor, temsirolimus and evaluation of circulating tumor cells and tumor biomarkers in persistent and recurrent epithelial ovarian and primary peritoneal malignancies: a gynecologic oncology group study. Gynecol Oncol 2011; 123: 19-26.
[27] Braun S, Schindlbeck C, Hepp F, Janni W, Kentenich C, Riethmuller G and Pantel K. Occult tumor cells in bone marrow of patients with locoregionally restricted ovarian cancer predict early distant metastatic relapse. J Clin Oncol 2001; 19: 368-375.
[28] Fehm T, Banys M, Rack B, Janni W, Marth C, Blassl C, Hartkopf A, Trope C, Kimmig R, Krawczyk N, Wallwiener D, Wimberger P and Kasimir-Bauer S. Pooled analysis of the prognostic relevance of disseminated tumor cells in the bone marrow of patients with ovarian cancer. Int J Gynecol Cancer 2013; 23: 839-845.
[29] Fehm T, Becker S, Bachmann C, Beck V, Gebauer G, Banys M, Wallwiener D and Solomayer EF. Detection of disseminated tumor cells in patients with gynecological cancers. Gynecol Oncol 2006; 103: 942-947.
[30] Judson PL, Geller MA, Bliss RL, Boente MP, Downs LS Jr, Argenta PA and Carson LF. Preoperative detection of peripherally circulating cancer cells and its prognostic significance in ovarian cancer. Gynecol Oncol 2003; 91: 389-394.
[31] Kolostova K, Matkowski R, Jedryka M, Soter K, Cegan M, Pinkas M, Jakabova A, Pavlasek J, Spicka J and Bobek V. The added value of circulating tumor cells examination in ovarian cancer staging. Am J Cancer Res 2015; 5: 3363-3375.
[32] Kuhlmann JD, Wimberger P, Bankfalvi A, Keller T, Scholer S, Aktas B, Buderath P, Hauch S, Otterbach F, Kimmig R and Kasimir-Bauer S. ERCC1-positive circulating tumor cells in the blood of ovarian cancer patients as a predictive biomarker for platinum resistance. Clin Chem 2014; 60: 1282-1289.
[33] Liu JF, Kindelberger D, Doyle C, Lowe A, Barry WT and Matulonis UA. Predictive value of circulating tumor cells (CTCs) in newly-diagnosed and recurrent ovarian cancer patients. Gynecol Oncol 2013; 131: 352-356.
[34] Obermayr E, Castillo-Tong DC, Pils D, Speiser P, Braicu I, Van Gorp T, Mahner S, Sehouli J, Vergote I and Zeillinger R. Molecular characterization of circulating tumor cells in patients with ovarian cancer improves their prognostic significance - a study of the OVCAD consortium. Gynecol Oncol 2013; 128: 15-21.
[35] Pearl ML, Zhao Q, Yang J, Dong H, Tulley S, Zhang Q, Golightly M, Zucker S and Chen WT. Prognostic analysis of invasive circulating tumor cells (iCTCs) in epithelial ovarian cancer. Gynecol Oncol 2014; 134: 581-590.

[36] Sang M, Wu X, Fan X, Sang M, Zhou X and Zhou N. Multiple MAGE-a genes as surveillance marker for the detection of circulating tumor cells in patients with ovarian cancer. Biomarkers 2013; 19: 34-42.
[37] Cui L, Kwong J and Wang CC. Prognostic value of circulating tumor cells and disseminated tumor cells in patients with ovarian cancer: a systematic review and meta-analysis. J Ovarian Res 2015; 8: 38.
[38] Zeng L, Liang X, Liu Q and Yang Z. The predictive value of circulating tumor cells in ovarian cancer. Int J Gynecol Cancer 2017; 27: 1109-1117.
[39] Zhou Y, Bian B, Yuan X, Xie G, Ma Y and Shen L. Prognostic value of circulating tumor cells in ovarian cancer: a meta-analysis. PLoS One 2015; 10: e0130873.
[40] Kleppe M, Wang T, Van Gorp T, Slangen BF, Kruse AJ and Kruitwagen RF. Lymph node metastasis in stages I and II ovarian cancer: a review. Gynecol Oncol 2011; 123: 610-614.
[41] Powless CA, Aletti GD, Bakkum-Gamez JN and Cliby WA. Risk factors for lymph node metastasis in apparent early-stage epithelial ovarian cancer: implications for surgical staging. Gynecol Oncol 2011; 122: 536-540.