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Original Article

Prognostic role of C-reactive protein in breast cancer: an updated systematic review and meta-analysis

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Abstract: The C-reactive protein (CRP), an inflammatory biomarker, has been identified to be related to progression of breast cancer. However, the results remain controversial. A meta-analysis of epidemiologic studies was therefore conducted to address this issue. Data were collected from studies comparing overall, cancer-specific, and disease-free survival (OS, CSS, and DFS) in patients with per natural log unit change in CRP. Study-specific risk estimates were pooled using a random-effects model. Sixteen studies involving a total of 15,545 breast cancer cases were included in this meta-analysis. The pooled results showed that per natural log unit change in CRP was significantly associated with poor OS (*HR* = 1.28, 95% *CI* = 1.13-1.44) and DFS (*HR* = 1.18, 95% *CI* = 1.04-1.34). For CSS, the pooled *HR* was 1.38 (95% *CI* = 1.15-1.66), which could strongly predict poorer survival in breast cancer patients. Similar results were also observed in the stratified analyses by number of patients, treatment, max follow-up and CRP marker. The meta-analysis indicated that elevated CRP levels has a critical prognostic value in patients with breast cancer as an inflammation biomarker.

Keywords: C-reactive protein, breast cancer, prognosis, meta-analysis

Introduction

Breast cancer is the most frequently diagnosed cancer among women and most common cancer-related death worldwide. According to data reported in 2012, about 1.67 million women were diagnosed with breast cancer and it was the most common cause of cancer-related death (522,000 deaths in 2012) [1]. And the number of breast cancer deaths will have increased to 846,587 by the year 2035 [1]. Multidisciplinary treatment strategies based on surgery, radiotherapy and chemotherapy have provided significant improvement in outcome of breast cancer patients. The tumor-node-metastasis (TNM) staging system and tumor markers, such as estrogen (ER) and progesterone (PR) receptors, and human epidermal growth factor receptor 2 (HER2), have made great contributions to the selection of treatment strategies [2]. However, approximately one third of patients with early stage breast cancer develop recurrence after operation or other additional therapies. In contrast, a similar proportion of node-positive patients remain free of distant metastases throughout the life [3]. Therefore, it is important for clinicians to find a simple and effective biomarker to provide advice on the selection of clinical strategies.

Notably, elevated levels of C-reactive protein (CRP), a systemic marker of chronic inflammation, have been associated with increased incidence as well as worse outcome in numerous types of cancer, such as gastro-oesophageal cancer, non-small cell lung cancer and prostate cancer [4-8]. However, longitudinal studies in women diagnosed with breast cancer have reported conflicting results in relation to inflammation and prognosis, with some studies showing an association between elevated CRP and poor prognosis [9-11] and others showing no relationship [12, 13].

During the last decade, several epidemiologic studies have evaluated the associations between CRP and breast cancer survival. A meta-analysis [14] published in 2011 found that higher CRP was statistically significantly associated with breast cancer overall survival (OS:

hazard ratio [*HR*] = 1.62, 95% confidence interval [*CI*]: 1.20-2.18), with a significant heterogeneity. However, most *HR*s extracted were calculated between the highest CRP concentration and the lowest, which means a big difference in CRP concentration and cut-off values among included studies. Besides, this estimate was based on only 4,502 breast cancer cases and lack of subgroup analysis. Thereafter, several epidemiologic studies with large sample sizes or long-term follow-up have been performed regarding CRP and breast cancer survival. Therefore, this meta-analysis is conducted to further clarify the association between a natural log unit increase in CRP levels and overall, cancer-specific, and disease-free survival (OS, CSS, and DFS) in breast cancer patients.

Material and methods

Literature search strategy

A systematic search up to 30 November 2015 was conducted in MEDLINE (via PubMed) and Excerpta Medica database (EMBASE) to identify relevant articles. Search terms included "C-reactive protein OR C reactive protein OR CRP", "breast cancer" combined with "prognosis OR prognostic OR survival". Additional relevant references cited in retrieved articles were also evaluated.

Inclusion and exclusion criteria

All papers were reviewed by two authors (S.Z. and Q.C.) independently. Uncertainties and discrepancies were resolved by consensus after discussing with a senior researcher (Q.P.). All studies included in the final meta-analysis satisfied the following criteria: (a) patients were pathologically diagnosed as female breast cancer; (b) the serum CRP level was measured before treatment; (c) breast cancer survival (OS, CSS or DFS) as the outcome of interest; (d) reported *HR* estimates with their corresponding 95% *CI* (or sufficient data to calculate of these effect measure), and (e) English articles. If the study was reported in duplication, the one published earlier or provided more detailed information was included. Review articles and editorials were included if they contained original data. Abstracts were excluded.

Quality assessment

According to a critical review checklist of the Dutch Cochrane Centre proposed by MOOSE, we strictly assessed the quality of all the studies included [15]. (i) clear definition of study population and origin of country; (ii) clear definition of study design; (iii) clear definition of outcome assessment, OS, CSS or DFS; (iv) clear definition of cut-off for CRP, and (v) sufficient period of follow-up. Otherwise, we would exclude the studies in order to ensure the quality of the meta-analysis.

Data extraction

Two of the authors (S.L. and S.Z.) performed the data extraction from each article and discrepancies were resolved by consensus. For studies meeting our inclusion criteria, a standardized data extraction form was used to extract the following data: the first author's name, year of publication, country of origin, study design, period of enrollment, the length of follow-up, characteristics of the studied population (sample size, age, stage of disease and treatment method), CRP measurement methods, and *HR* estimates (for OS, CSS or DFS) with corresponding 95% *CI*s for CRP as a continuous variable or at least 3 categories of CRP levels. Multivariate Cox proportional hazards regression analysis was used in the present analysis. When data for *HR* was not available, we extracted the total numbers of observed deaths and the numbers of patients in each group to calculate *HR* [16]. Data were extracted by Engauge Digitizer version 4.1 (http://digitizer.sourceforge.net/) from the graphical survival plots when data were only available as Kaplan-Meier curves [17], then the estimation of the *HR* was performed by the described method [16].

Statistical analysis

The *HR* per natural log unit change in CRP with 95% *CI* was used to compute the pooled *HR* of elevated CRP levels and the OS, CSS or DFS in breast cancer patients. A fix-effect or random-effect model was used to pool the data, based on the Mantel-Haenszel method [18] and the DerSimonian and Laird method [19], respectively. These two models provide similar results when between-studies heterogeneity is absent; otherwise, random-effect model is more appropriate. Several studies did not report a risk estimate for one unit change in ln (CRP). For these studies, we used the method proposed by Orsini [20] and Greenland [21] to estimate the ln (*HR*) for one unit increase in ln (CRP).

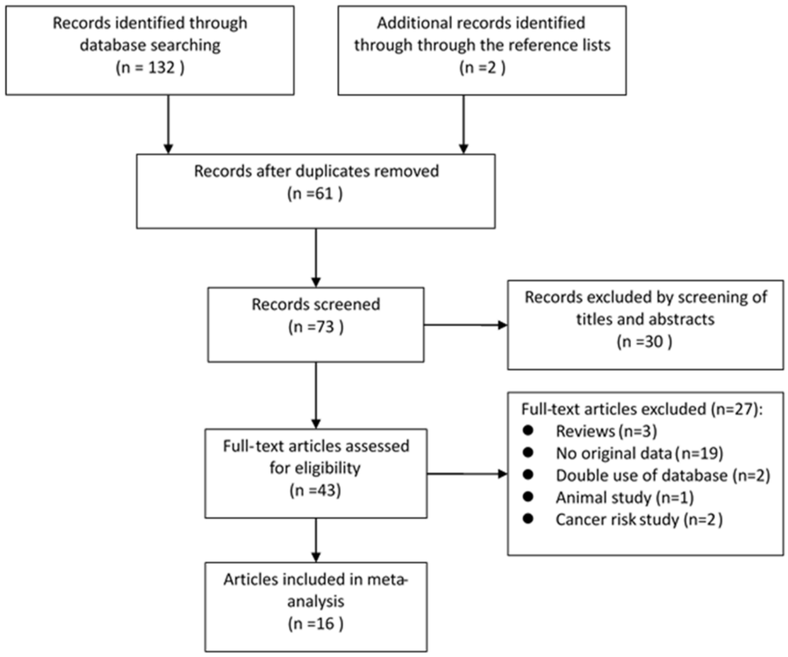


Figure 1. Flow diagram of systematic literature search.

Cochrane *Q* test (*P* < 0.10 indicated a high level of statistical heterogeneity) and I^2 (values of 25%, 50% and 75% corresponding to low, moderate and high degrees of heterogeneity, respectively) was used to assess the heterogeneity between eligible studies, which test total variation across studies that was attributable to heterogeneity rather than to chance [22]. Subgroup analyses for one unit increase in ln (CRP) and the OS, CSS or DFS in breast cancer patients were subsequently carried out according to the study type, geographical region, number of patients, treatment, max follow-up time, CRP markers, ER or PR status, regression method and source of *HR*. Sensitivity analysis was also conducted to assess the influence of each individual study on the strength and stability of the meta-analytic results. Each time, one study in the meta-analysis was excluded to show that study's impact on the combined effect size. Funnel plot and Begg adjusted rank correlation test for funnel plot asymmetry were performed to test any existing publication bias.

All statistical analyses were performed using STATA version 12 for Windows (StataCorp LP, College Station, TX, USA). A two-tailed *P* < 0.05 was considered statistically significant.

Results

Literature search

As shown in **Figure 1**, the search strategy generated 134 citations, of which 43 were considered of potential value after screening of titles and abstracts and the full text was retrieved for detailed evaluation. Twenty seven of these 43 articles were subsequently excluded from the meta-analysis for various reasons, including 3 were reviews, 1 was animal study, 19 that did not provide *HR* or datas to calculate it, 2 were double use of database and 2 were cancer risk study. So, 16 studies were eligible and included in this systematic review and meta-analysis [9-13, 23-33].

Characteristics of the selected studies

Individual characteristics of the included 16 studies are summarised in **Table 1**. They were published from 1982 to 2015 and involved a total of 15,545 breast cancer cases. Among these studies, 9 studies were conducted in Europe [10-13, 23, 25, 27, 30, 31], 4 in North America [9, 28, 29, 32], and 3 in Asia [24, 26, 33]. Of all the selected studies, 11 presented *HR*s [9, 10, 12, 25-31, 33], while in the other 5 studies [11, 13, 23, 24, 32], *HR*s were absent, and we needed to ask authors or calculate the *HR*s from the available data or survival curves. Three studies [11, 26, 27] did not give accurate data for follow-up. The median follow-up period of all studies ranged from 0 to 204 months.

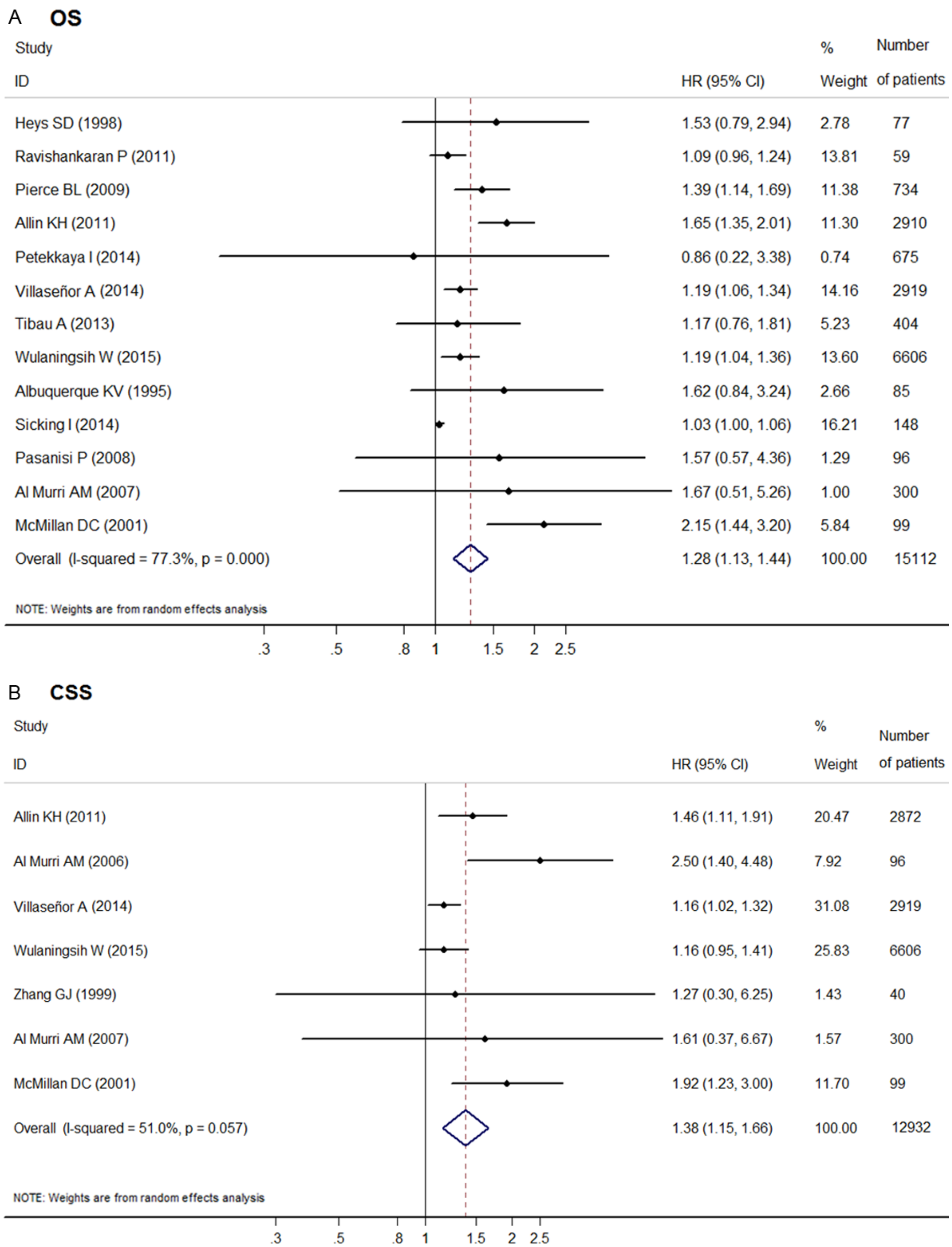
Results of the meta-analysis

Overall survival: Thirteen studies reported the relationship between serum CRP levels and OS in breast cancer patients. Among the studies included, one showed an insignificant negative association between one unit change in ln (CRP) and OS in breast cancer patients, and the other twelve showed positive associations, six

Table 1. Characteristics of the included studies

First author	Year	Year of recruitment	Country	No. of Patients	Age, y	Disease	Markers	Survival analysis	Hazard ratio	Median follow-up period (months)
Heys SD	1998	NA	UK	77	47 (30-73)	Locally advanced BC	CRP	OS	Survival curve	31 (24-38)
Ravishankaran P	2011	NA	India	59	59.11 (36-85)	BC	CRP	OS	Data extrapolated	36
Pierce BL	2009	1995-1999	USA	734	57.5±10.4	BC	Hs-CRP	OS, DFS	Report	83
Allin KH	2011	2002-2009	Denmark	2910	48-74	BC	Hs-CRP	OS, CSS, DFS	Report	36 (0-84)
Al Murri AM	2006	2002-2004	UK	96	(< 50/> 50) 21/75	Metastatic BC	CRP	CSS	Report	16 (7-)
Petekkaya I	2014	2009-2012	Turkey	675	50 (25-92)	Operable BC	CRP	OS, DFS	Report	NA
Villaseñor A	2014	1995-2000	USA	2919	53	BC	Hs-CRP	OS, CSS, DFS	Report	87.6
Tibau A	2013	1989-1996	Canada	404	50.5	BC	Hs-CRP	OS, DFS	Report	145.2 (2.4-204)
Wulaningsih W	2015	1985-1996	Sweden	6606	50.33±11.56	BC	CRP	OS, CSS	Report	11.72±5.48
Albuquerque KV	1995	NA	UK	85	60.52±12.22	Metastatic BC	CRP	OS	Survival curve	NA
Sicking I	2014	1985-2004	Germany	148	62 (40-90)	Node-negative BC	CRP	OS, DFS	Report	113
Mortensen RF	1982	NA	USA	297	NA	BC	CRP	DFS	Survival curve	3-48
Pasanisi P	2008	NA	Italy	96	56.8±5.6	BC	CRP	OS	Author provided	66
Zhang GJ	1999	NA	Japan	40	54 (32-74)	Metastatic BC	CRP	CSS	Report	32 (3-110)
Al Murri AM	2007	2001-2003	UK	300	(< 50/> 50) 67/233	Primary operable BC	CRP	OS, CSS, DFS	Report	46
McMillan DC	2001	1988-1996	UK	99	59 (29-89)	BC	CRP	OS, CSS	Report	NA

Abbreviations: BC, breast cancer; CRP, C-reactive protein; Hs-CRP, High-sensitivity C-reactive protein; OS, overall survival; CSS, cancer-specific survival; DFS, disease-free survival; NA, not available.


A OS
Study ID
HR (95% CI)
% Weight
Number of patients
Heys SD (1998) 1.53 (0.79, 2.94) 2.78 77
Ravishankaran P (2011) 1.09 (0.96, 1.24) 13.81 59
Pierce BL (2009) 1.39 (1.14, 1.69) 11.38 734
Allin KH (2011) 1.65 (1.35, 2.01) 11.30 2910
Petekkaya I (2014) 0.86 (0.22, 3.38) 0.74 675
Villaseñor A (2014) 1.19 (1.06, 1.34) 14.16 2919
Tibau A (2013) 1.17 (0.76, 1.81) 5.23 404
Wulaningsih W (2015) 1.19 (1.04, 1.36) 13.60 6606
Albuquerque KV (1995) 1.62 (0.84, 3.24) 2.66 85
Sicking I (2014) 1.03 (1.00, 1.06) 16.21 148
Pasanisi P (2008) 1.57 (0.57, 4.36) 1.29 96
Al Murri AM (2007) 1.67 (0.51, 5.26) 1.00 300
McMillan DC (2001) 2.15 (1.44, 3.20) 5.84 99
Overall (I-squared = 77.3%, p = 0.000) 1.28 (1.13, 1.44) 100.00 15112
NOTE: Weights are from random effects analysis
.3 .5 .8 1 1.5 2 2.5
B CSS
Study ID
HR (95% CI)
% Weight
Number of patients
Allin KH (2011) 1.46 (1.11, 1.91) 20.47 2872
Al Murri AM (2006) 2.50 (1.40, 4.48) 7.92 96
Villaseñor A (2014) 1.16 (1.02, 1.32) 31.08 2919
Wulaningsih W (2015) 1.16 (0.95, 1.41) 25.83 6606
Zhang GJ (1999) 1.27 (0.30, 6.25) 1.43 40
Al Murri AM (2007) 1.61 (0.37, 6.67) 1.57 300
McMillan DC (2001) 1.92 (1.23, 3.00) 11.70 99
Overall (I-squared = 51.0%, p = 0.057) 1.38 (1.15, 1.66) 100.00 12932
NOTE: Weights are from random effects analysis
.3 .5 .8 1 1.5 2 2.5

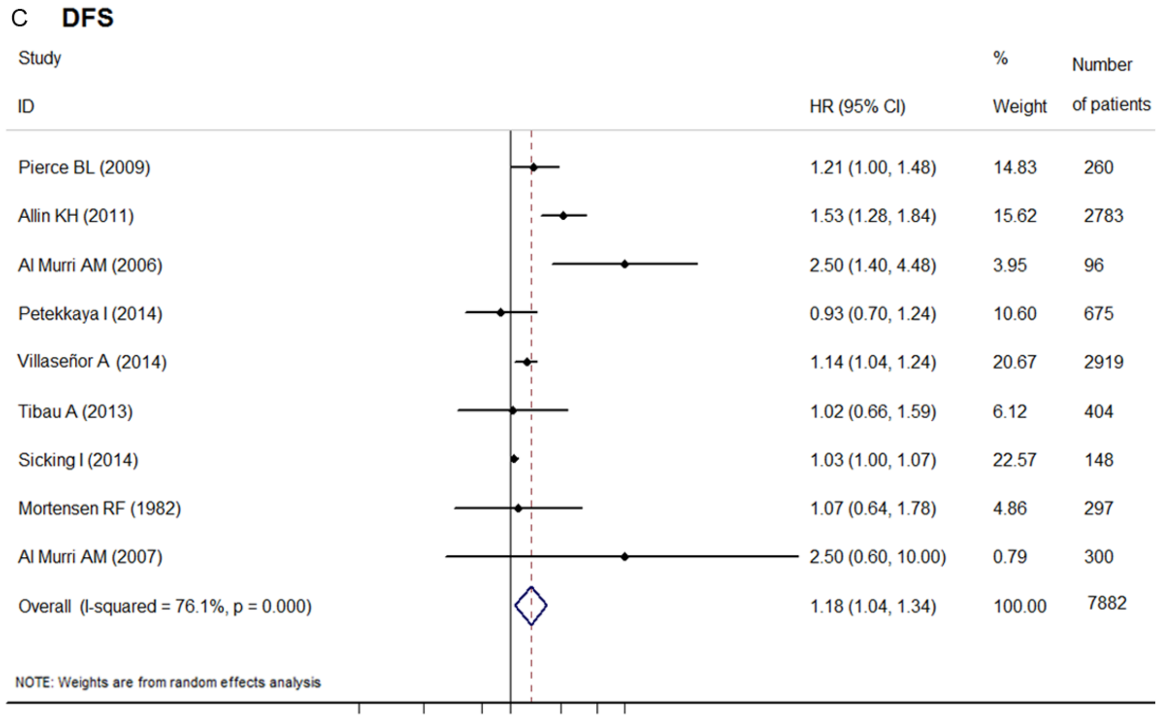


Figure 2. Forest plot for the association between per log-transformed CRP concentration and female breast cancer prognosis. Survival data are reported as overall survival (A), cancer-specific survival (B), and disease-free survival (C).

of which showed statistical significance. The heterogeneity test indicated there was high degree of heterogeneity among included studies (Q-test $P_{heterogeneity}$ = 0.000, I^2 = 77.3%), thus a random effects model was employed to obtain the pooled *HR*. The statistical result showed that per natural log unit change in CRP was significantly correlated with poor OS (*HR* = 1.28, 95% *CI*: 1.13-1.44) (**Figure 2A**).

Cancer-specific survival: Seven studies reported the relationship between serum CRP level and CSS in breast cancer patients. All the studies included showed positive associations between one unit change in ln (CRP) and CSS in breast cancer patients, four of which showed statistical significance. The heterogeneity test indicated there was moderate degree of heterogeneity among included studies (Q-test $P_{heterogeneity}$ = 0. 057, I^2 = 51.0%), thus a random effects model was employed to obtain the pooled *HR*. The statistical result showed that per natural log unit change in CRP was significantly correlated with poor CSS (*HR* = 1.38, 95% *CI*: 1.15-1.66) (**Figure 2B**).

Disease-free survival: Nine studies reported the relationship between serum CRP levels and DFS in breast cancer patients. Among the studies included, one showed an insignificant negative association between one unit change in ln (CRP) and CSS in breast cancer patients, and the other eight showed positive associations, five of which showed statistical significance. The heterogeneity test indicated there was high degree of heterogeneity among included studies (Q-test $P_{heterogeneity}$ = 0.000, I^2 = 76.1%), thus a random effects model was employed to obtain the pooled *HR*. The statistical result showed that per natural log unit change in CRP was significantly correlated with poor DFS (*HR* = 1.18, 95% *CI*: 1.04-1.34) (**Figure 2C**).

Subgroup analyses

Table 2 presents detailed results of subgroup analyses. The associations of ln (CRP) with poor OS in breast cancer patients did not differ by number of patients, treatment, max follow-up, CRP markers and ER status. Elevated CRP levels were significantly associated with poor

Table 2. Results of subgroup analyses

Group	OS			CSS			DFS		
	No. of study	*HR* (95% *CI*)	I^2, % †	No. of study	*HR* (95% *CI*)	I^2, % †	No. of study	*HR* (95% *CI*)	I^2, % †
All	13	1.28 (1.13-1.44)	77.3	7	1.38 (1.15-1.66)	51.0	9	1.18 (1.04-1.34)	76.1
Study type									
Prospective	11	1.22 (1.09-1.37)	74.8	4	1.20 (1.08-1.32)	0.0	8	1.15 (1.02-1.29)	72.1
Geographic region									
Europe	8	1.41 (1.14-1.75)	54.7	5	1.54 (1.18-2.03)	57.0	4	1.50 (1.02-2.19)	89.2
North America	3	1.24 (1.12-1.36)	0.0	1	\		4	1.15 (1.06-1.24)	0.0
Asia	2	1.09 (0.96-1.24)	0.0	1	\		1	\	
Number of patients									
< 300	6	1.24 (1.03-1.49)	71.0	3	2.06 (1.46-2.91)	0.0	4	1.21 (0.96-1.53)	73.5
≥ 300	7	1.30 (1.16-1.46)	41.2	4	1.20 (1.08-1.32)	0.0	5	1.19 (0.97-1.46)	68.4
Treatment									
Multiple	9	1.15 (1.05-1.26)	59.3	5	1.26 (1.03-1.53)	39.8	7	1.12 (1.00-1.25)	65.4
Others	4	1.73 (1.46-2.05)	0.0	2	1.58 (1.24-2.01)	5.5	2	1.39 (1.02-1.90)	40.1
Max follow-up									
< 5 years	7	1.30 (1.08-1.57)	50.6	4	1.66 (1.08-2.55)	66.8	5	1.27 (0.94-1.72)	61.4
≥ 5 years	6	1.27 (1.06-1.51)	85.5	3	1.23 (1.06-1.42)	11.3	4	1.17 (1.00-1.36)	85.8
Marker									
Hs-CRP	4	1.35 (1.14-1.60)	64.1	2	1.26 (1.01-1.56)	55.6	4	1.24 (1.06-1.45)	65.6
CRP	9	1.20 (1.05-1.37)	63.2	5	1.62 (1.10-2.38)	55.7	5	1.17 (0.90-1.53)	63.5
ER status									
ER+	2	1.40 (1.13-1.72)	0.0		\			\	
ER-	2	2.20 (1.41-3.41)	0.0		\			\	
PR status									
PR+	2	1.69 (1.08-2.64)	44.6		\			\	
PR-	2	1.60 (0.86-3.00)	68.5		\			\	
ER/PR status									
ER+/PR+	2	1.43 (1.11-1.83)	0.0		\		2	1.08 (0.80-1.41)	0.0
ER-/PR-	2	1.00 (0.23-4.39)	81.0		\		2	0.83 (0.21-3.19)	69.8
Regression method									
Univariate	4	1.12 (0.99-1.26)	0.0	1	\		3	1.30 (0.75-2.26)	77.7
Multivariate	9	1.31 (1.13-1.53)	84.0	6	1.27 (1.11-1.45)	24.6	6	1.18 (1.04-1.35)	79.4
Source of *HR*									
Reported	11	1.26 (1.12-1.43)	80.1	7	1.38 (1.15-1.66)	51.0	8	1.19 (1.04-1.36)	79.1
Estimated	2	1.57 (0.98-2.52)	0.0	0	\		1	\	

Abbreviation: OS, overall survival; CSS, cancer-specific survival; DFS, disease-free survival; Hs-CRP, High-sensitivity C-reactive protein; ER, estrogen receptors; PR, progesterone receptors; *HR*, hazard ratio; *CI*, confidence intervals; † I^2 is interpreted as the proportion of total variation across studies that are due to heterogeneity rather than chance.

OS in breast cancer patients in Europe (*HR* = 1.41, 95% *CI*: 1.14-1.75) and North America (*HR* = 1.24, 95% *CI*: 1.12-1.36), but not in Asia (*HR* = 1.09, 95% *CI*: 0.96-1.24). When cancer cases stratified by ER and PR status, the association was significantly for ER+ group (*HR* = 1.40, 95% *CI*: 1.13-1.72), PR+ group (*HR* = 1.69, 95% *CI*: 1.08-2.64) and ER+/PR+ group (*HR* = 1.43, 95% *CI*: 1.11-1.83), but not for ER-, PR- and ER-/PR- group.

The associations of ln (CRP) with poor CSS in breast cancer patients did not differ by number of patients, treatment, max follow-up and CRP markers.

The associations of ln (CRP) with poor DFS in breast cancer patients did not differ by geographic region and treatment, however, the association disappeared when stratified by number of patients and ER/PR status. When

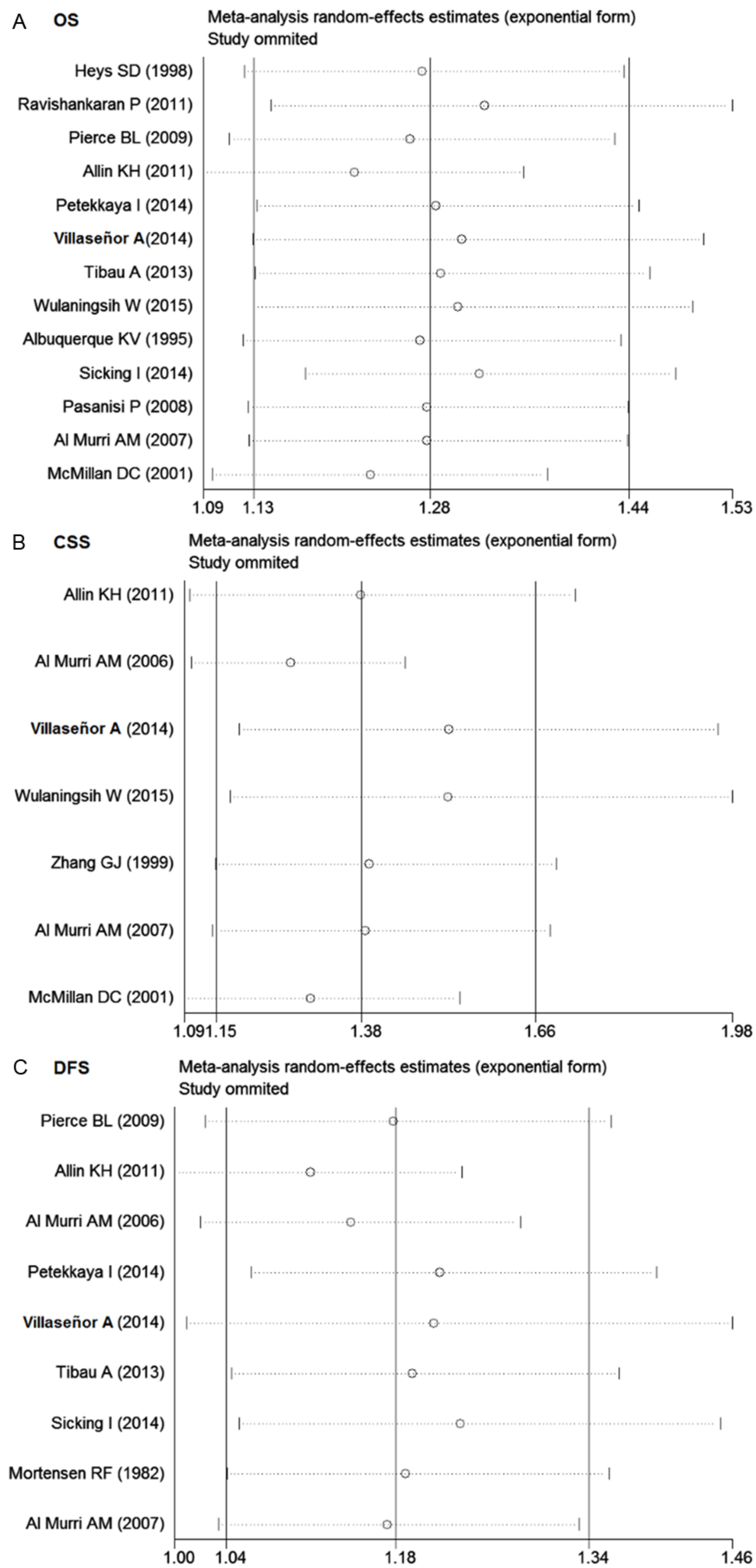


Figure 3. Influence analyses for omitting individual study on the summary *HR*. Survival data are reported as overall survival (A), cancer-specific survival (B), and disease-free survival (C).

cancer cases stratified by max follow-up period, the association was significantly for "≥5 years" group (*HR* = 1.17, 95% *CI*: 1.00-1.36), but not for "< 5 years" group (*HR* = 1.27, 95% *CI*: 0.94-1.72). Elevated CRP levels were significantly associated with poor DFS in breast cancer patients for Hs-marker (*HR* = 1.24, 95% *CI*: 1.06-1.45), but not for traditional CRP (*HR* = 1.17, 95% *CI*: 0.90-1.53).

In short, the estimated heterogeneity (OS, CSS and DFS) for studies included decreased to some degree but did not obliterate.

Influence analysis of individual studies

To address the potential bias due to the quality of the included studies, we performed the sensitivity analysis by calculating pooled *HR*s again when omitting one study at a time. **Figure 3A-C** showed the results of sensitivity analysis for OS, CSS and DFS respectively. The pooled *HR*s per natural log unit change in CRP for OS in breast cancer patients ranged from 1.22 (95% *CI*: 1.09-1.36) to 1.32 (95% *CI*: 1.15-1.53). The pooled *HR*s per natural log unit change in CRP for CSS in breast cancer patients ranged from 1.27 (95% *CI*: 1.11-1.45) to 1.52 (95% *CI*: 1.18-1.95). The pooled *HR*s per natural log unit change in CRP for DFS in breast cancer patients ranged from 1.11 (95% *CI*: 1.00-1.24) to 1.24 (95% *CI*: 1.05-1.45). The meta-analysis result of the pooled

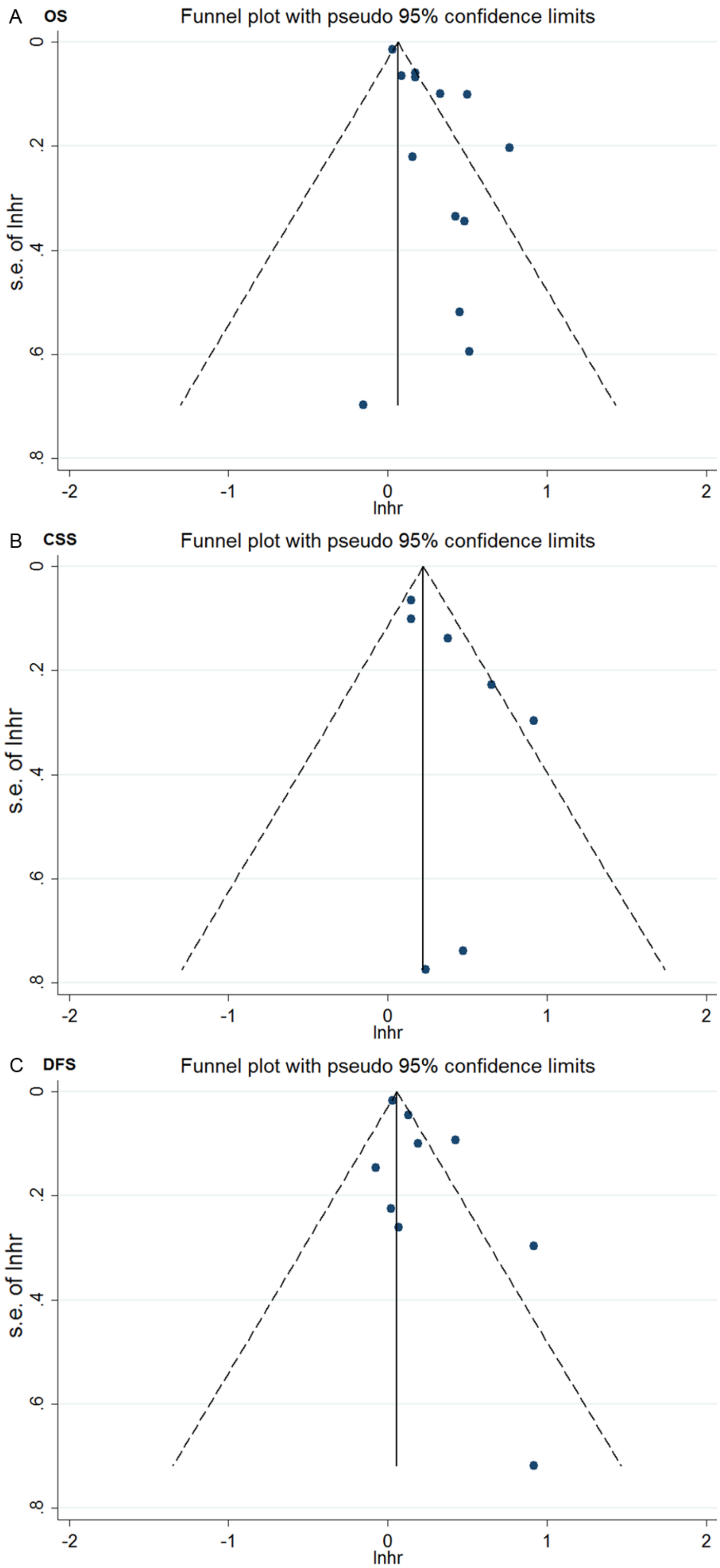


Figure 4. Funnel plots for publication bias of overall survival (A), cancer-specific survival (B), and disease-free survival (C).

*HR*s per natural log unit change in CRP for OS, CSS and DFS in breast cancer patients were not significantly affected by omission of any of the individual studies analysed, which indicated that each single study didn't influence the stability of pooled *HR* estimate.

Publication bias

There was no evidence of publication bias as demonstrated by the non-significant *P* values of Begg's test for OS (0.625), CSS (0.293) and DFS (0.677), and the near-symmetric funnel plot (**Figure 4A-C**).

Discussion

This meta-analysis indicated that a natural log unit increase in CRP levels could predict worse survival in patients with breast cancer. The data showed that CRP was associated with OS, CSS, and DFS. Elevated level of CRP could be a strong prognostic factor for CSS. Sensitivity analysis further confirmed the robustness of these results.

Our summary estimate of CRP and breast cancer survival were consistent with a previous meta-analysis study [14]. This meta-analysis which included 10 studies with only 4,502 cases showed that, compared with the lowest concentration of CRP level, the highest group was significantly associated with poor OS (*HR* = 1.62, 95% *CI*: 1.20-2.18), CSS (*HR* = 2.08, 95% *CI*: 1.48-2.94) and DFS (*HR* = 1.81, 95% *CI*: 1.44-2.26). However, the results were doubtful with a big difference in CRP concentration and cut-off values among included studies. In contrast to that study, our meta-analysis involved a total of 15,545 breast cancer cases and used the method proposed by Orsini [20] and Greenland [21] to estimate the ln(*HR*) for one unit increase in ln (CRP), which decreased the influence caused by CRP concentration and cut-off values.

Results from subgroup analyses showed that geographic region, number of patients, treatment and CRP markers might be possible sources of heterogeneity. Despite suffering the limitations of observational nature, several findings from subgroup-analysis deserved to be notable. Per natural log unit change in CRP was not significantly associated with poor OS in Asia, which means regional differences may exist between the elevated levels of CRP and OS in breast cancer patients. However, the pooled *HR* from Asia were only from two countries, India and Turkey. As known to all, China has the largest number of breast cancer patients in Asia [34]. So we should be cautious with the representativeness of these included studies. Results from subgroup analyses stratified by source of ER/PR status showed that the elevated levels of CRP was significantly associated with poor OS in PR+ or ER+/PR+ breast cancer patients, not in PR- or ER-/PR- breast cancer patients. However, the results were only from two studies. So, more studies are therefore needed to confirm the function of ER/PR status between serum CRP and OS, CSS or DFS in the future. Besides, Hs-CRP, as an inflammatory biomarker, is superior to common CRP in predicting risk of OS, CSS and DFS in breast cancer patients.

The present study has several strengths. First, it included a large sample size (15,545 breast cancer cases). Second, we applied a rigorous inclusion/exclusion criterion, fully outcomes of interest (OS, CSS, and DFS) and advanced meta-analysis of *HR* for survival. Moreover, more comparable dose-response relationship were created for each study, and subgroup analyses stratified by the study type, geographical region, number of patients, treatment, max follow-up time, CRP markers, ER or PR status, regression method and source of *HR* were conducted. Thus, the effect of potential confounders was minimized. In addition, no publication bias were observed in our analyses, combined with the results of sensitivity analysis, indicating that our results are robust.

However, the present meta-analysis has several limitations. First, the methods for detecting serum CRP varied from studies, mainly including turbidimetric immunoassay, latex photometric immunoassay, and enzyme linked immunosorbent assay (ELISA). Second, significant heterogeneity was observed. To address this issue, the random-effects model meta-analysis was reported to combine data whenever significant heterogeneity was noted. We used appropriate well-motivated inclusion criteria to maximize homogeneity, and performed sensitivity and subgroup analyses to investigate potential sources of heterogeneity. Finally, the CRP is usually regarded as a prognostic marker in several diseases which are related to survival, such as cardiovascular diseases [35]. Thus, we cannot consider CRP as a 'predictor' for survival unless the involved patients do not have other severe diseases related to CRP. Because the presence or absence of concomitant severe diseases was not mentioned in most of selected studies, we should be careful while considering CRP as a predictor of survival in cancer patients.

In conclusion, CRP as a role of representative cost-effective and non-invasive biomarker for systemic inflammatory response has a significant impact in predicting outcomes of breast cancer. The findings of this meta-analysis indicated that elevated CRP levels was associated with poor breast cancer survival, and CRP was a strong predictor for all three survival outcomes (OS, CSS and DFS), especially for CSS. Our meta-analysis has provided a better understanding of the association between the presence of systemic inflammatory response and cancer progression, and novel anti-inflammatory therapeutics that target the tumor microenvironment might also be considered in the future.

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Disclosure of conflict of interest

None.

Authors' contribution

All authors have made substantial contributions to the conception and design of the study. L.G. contributed to protocol design, search, data extraction, quality assessment, statistical analysis, and writing the report. S.L. and S.Z contributed to protocol design, search, data extraction, and writing the report. Q.C., M.Z. and P.Q. contributed to quality assessment, statistical analysis, and revision of the report. X.S. contributed to interpretation of data and revision of the report. All authors have seen and approved the final version.

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References

[1] Ervik M, Lam F, Ferlay J, Mery L, Soerjomataram I, Bray F. Cancer Today. Lyon, France: International Agency for Research on Cancer. Cancer Today 2016; Available from: http://gco.iarc.fr/today, accessed [15/05/2016].

[2] Kaufmann M and Pusztai L. Use of standard markers and incorporation of molecular markers into breast cancer therapy: Consensus recommendations from an International Expert Panel. Cancer 2011; 117: 1575-1582.

[3] Feng Y, Sun B, Li X, Zhang L, Niu Y, Xiao C, Ning L, Fang Z, Wang Y, Zhang L, Cheng J, Zhang W and Hao X. Differentially expressed genes between primary cancer and paired lymph node metastases predict clinical outcome of node-positive breast cancer patients. Breast Cancer Res Treat 2007; 103: 319-329.

[4] Guo L, Liu S, Zhang S, Chen Q, Zhang M, Quan P, Lu J and Sun X. C-reactive protein and risk of breast cancer: A systematic review and meta-analysis. Sci Rep 2015; 5: 10508.

[5] Allin KH, Bojesen SE and Nordestgaard BG. Baseline C-reactive protein is associated with incident cancer and survival in patients with cancer. J Clin Oncol 2009; 27: 2217-2224.

[6] Crumley AB, McMillan DC, McKernan M, Going JJ, Shearer CJ and Stuart RC. An elevated C-reactive protein concentration, prior to surgery, predicts poor cancer-specific survival in patients undergoing resection for gastro-oesophageal cancer. Br J Cancer 2006; 94: 1568-1571.

[7] Scott HR, McMillan DC, Forrest LM, Brown DJ, McArdle CS and Milroy R. The systemic inflammatory response, weight loss, performance status and survival in patients with inoperable non-small cell lung cancer. Br J Cancer 2002; 87: 264-267.

[8] McArdle PA, Mir K, Almushatat AS, Wallace AM, Underwood MA and McMillan DC. Systemic inflammatory response, prostate-specific antigen and survival in patients with metastatic prostate cancer. Urol Int 2006; 77: 127-129.

[9] Pierce BL, Ballard-Barbash R, Bernstein L, Baumgartner RN, Neuhouser ML, Wener MH, Baumgartner KB, Gilliland FD, Sorensen BE, McTiernan A and Ulrich CM. Elevated biomarkers of inflammation are associated with reduced survival among breast cancer patients. J Clin Oncol 2009; 27: 3437-3444.

[10] Al Murri AM, Bartlett JM, Canney PA, Doughty JC, Wilson C and McMillan DC. Evaluation of an inflammation-based prognostic score (GPS) in patients with metastatic breast cancer. Br J Cancer 2006; 94: 227-230.

[11] Albuquerque KV, Price MR, Badley RA, Jonrup I, Pearson D, Blamey RW and Robertson JF. Pre-treatment serum levels of tumour markers in metastatic breast cancer: a prospective assessment of their role in predicting response to therapy and survival. Eur J Surg Oncol 1995; 21: 504-509.

[12] Al Murri AM, Wilson C, Lannigan A, Doughty JC, Angerson WJ, McArdle CS and McMillan DC. Evaluation of the relationship between the systemic inflammatory response and cancer-specific survival in patients with primary operable breast cancer. Br J Cancer 2007; 96: 891-895.

[13] Pasanisi P, Venturelli E, Morelli D, Fontana L, Secreto G and Berrino F. Serum insulin-like growth factor-I and platelet-derived growth factor as biomarkers of breast cancer prognosis. Cancer Epidemiol Biomarkers Prev 2008; 17: 1719-1722.

[14] Han Y, Mao F, Wu Y, Fu X, Zhu X, Zhou S, Zhang W, Sun Q and Zhao Y. Prognostic role of C-reactive protein in breast cancer: a systematic review and meta-analysis. Int J Biol Markers 2011; 26: 209-215.

[15] Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA and Thacker SB. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA 2000; 283: 2008-2012.

[16] Parmar MK, Torri V and Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. Stat Med 1998; 17: 2815-2834.
[17] 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.
[18] Mantel N and Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst 1959; 22: 719-48.
[19] DerSimonian R and Kacker R. Random-effects model for meta-analysis of clinical trials: an update. Contemp Clin Trials 2007; 28: 105-114.
[20] Orsini N, Bellocco R and Greenland S. Generalized least squares for trend estimation of summarized dose-response data. Stata Journal 2006; 6: 40.
[21] Greenland S and Longnecker MP. Methods for trend estimation from summarized dose-response data, with applications to meta-analysis. Am J Epidemiol 1992; 135: 1301-1309.
[22] Higgins JPT and Thompson SG. Quantifying heterogeneity in a meta-analysis. Statistics in Medicine 2002; 21: 1539-1558.
[23] Heys SD, Ogston KN, Simpson WG, Walker LG, Hutcheon AW, Sarkar TK and Eremin O. Acute phase proteins in patients with large and locally advanced breast cancer treated with neoadjuvant chemotherapy: response and survival. Int J Oncol 1998; 13: 589-594.
[24] Ravishankaran P and Karunanithi R. Clinical significance of preoperative serum interleukin-6 and C-reactive protein level in breast cancer patients. World J Surg Oncol 2011; 9: 18.
[25] Allin KH, Nordestgaard BG, Flyger H and Bojesen SE. Elevated pre-treatment levels of plasma C-reactive protein are associated with poor prognosis after breast cancer: a cohort study. Breast Cancer Res 2011; 13: R55.
[26] Petekkaya I, Aksoy S, Roach EC, Okoh AK, Gecmez G, Gezgen G, Isler DC, Dogan E, Babacan T, Sarici F, Petekkaya E and Altundag K. Impact of inflammatory markers on the prognosis of patients with operable breast cancer. J BUON 2014; 19: 673-680.
[27] McMillan DC, Elahi MM, Sattar N, Angerson WJ, Johnstone J and McArdle CS. Measurement of the systemic inflammatory response predicts cancer-specific and non-cancer survival in patients with cancer. Nutr Cancer 2001; 41: 64-69.
[28] Villasenor A, Flatt SW, Marinac C, Natarajan L, Pierce JP and Patterson RE. Postdiagnosis C-reactive protein and breast cancer survivorship: findings from the WHEL study. Cancer Epidemiol Biomarkers Prev 2014; 23: 189-199.
[29] Tibau A, Ennis M and Goodwin PJ. Post-surgical highly sensitive C-reactive protein and prognosis in early-stage breast cancer. Breast Cancer Res Treat 2013; 141: 485-493.
[30] Wulaningsih W, Holmberg L, Garmo H, Malmstrom H, Lambe M, Hammar N, Walldius G, Jungner I and Van Hemelrijck M. Prediagnostic serum inflammatory markers in relation to breast cancer risk, severity at diagnosis and survival in breast cancer patients. Carcinogenesis 2015; 36: 1121-1128.
[31] Sicking I, Edlund K, Wesbuer E, Weyer V, Battista MJ, Lebrecht A, Solbach C, Grinberg M, Lotz J, Hoffmann G, Rahnenfuhrer J, Hengstler JG and Schmidt M. Prognostic influence of pre-operative C-reactive protein in node-negative breast cancer patients. PLoS One 2014; 9: e111306.
[32] Mortensen RF and Rudczynski AB. Prognostic significance of serum CRP levels and lymphoid cell infiltrates in human breast cancer. Oncology 1982; 39: 129-133.
[33] Zhang GJ and Adachi I. Serum interleukin-6 levels correlate to tumor progression and prognosis in metastatic breast carcinoma. Anticancer Res 1999; 19: 1427-1432.
[34] Zhang SK, Guo LW, Chen Q, Zhang M, Liu SZ, Quan PL, Lu JB and Sun XB. The association between human papillomavirus 16 and esophageal cancer in Chinese population: a meta-analysis. BMC Cancer 2015; 15: 1096.
[35] Rietzschel E and De Buyzere M. High-sensitive C-reactive protein: universal prognostic and causative biomarker in heart disease? Biomark Med 2012; 6: 19-34.