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Review Article

Roles of detection methods in predicting breast cancer survival: a pooled analysis of 57,542 patients

Xiaoqing Fan[1,2], Gang Liu[2], Weimin Zhou[3], Guobao Liu[4]

[1]Jiangxi Medical College of Nanchang University, Nanchang 330006, Jiangxi Province, China; [2]Department of Breast Surgery, The Third Hospital of Nanchang City, Key Laboratory of Breast Diseases, Nanchang 330009, Jiangxi Province, China; [3]Department of Vascular Surgery, The Second Affiliated Hospital of Nanchang University, Nanchang 330006, Jiangxi Province, China; [4]Department of Radiology, The 908th Hospital of Chinese PLA Joint Logistic Support Force, Yingtan 335000, Jiangxi Province, China

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Abstract: Objectives: The aim of this study was to investigate breast cancer survival rates and risk of breast cancer using different detection modes (screening, symptomatic, interval, and outside screening). Methods: PubMed, EMBASE, and Web of Science were systematically searched through August 2018. Hazard ratios (HR) and odds ratio (OR) with 95% confidence intervals (CI) were pooled using Review Manager Version 5.3. Results: Fifteen randomized controlled studies, including 57,542 patients with breast cancer, were analyzed. Pooled analysis indicated that the mode of screening-detection was associated with survival outcomes of breast cancer patients, whereas the combined HR of other detection modes (symptomatic, interval, and outside screening) was associated with poor survival, according to univariable analysis (HR = 2.78; 95% CI, 2.38-3.24, P<0.00001) and multivariable analysis (HR = 1.60; 95% CI, 1.43-1.79, P<0.00001), using a random-effects model. This study also found that the screening-detection mode showed a significantly higher risk of ER (OR = 1.58, 95% CI [1.31, 1.91]) and PR (OR = 1.43, 95% CI [1.33, 1.53]), but lower risk of HER2 (OR = 0.75, 95% CI [0.67, 0.83]) and Ki67 index (OR = 0.57, 95% CI [0.45, 0.73]), compared with other detection modes in patients suffering from breast cancer. Conclusion: Breast cancer detected by screening-detection is an independent prognostic factor. It is associated with a more favorable prognosis than in patients diagnosed using outside screening programs.

Keywords: Screening, breast cancer, prognosis, survival analysis

Introduction

Although there have been some improvements in diagnosis and therapies of various human cancers, breast cancer remains the leading cause of cancer-related mortality among women worldwide. It is, therefore, a major public health threat [1, 2]. According to cancer statistics, breast cancer is the most commonly diagnosed cancer and the leading cause of cancer-related deaths in women [2, 3].

Breast cancer detected by mammography has increased due to its expanding use. This natural course, especially for early breast cancer, has changed as a result of the introduction of mammographic screening [4]. Human breast cancer screening with mammography has shown reductions in mortality from the disease, according to population-based randomized controlled trials [5, 6]. Screening with mammography often detects breast cancer at earlier stages. The screening-detection mode with breast cancer is, therefore, often associated with improved prognosis, compared with other detection modes (including interval, symptomatic, and outside screening) [7, 8]. The method of screening-detected breast cancer has been defined according to true attendance at mammography screenings. In other words, other patients, including cancer patients that did not undergo mammography, are considered as other detection modes (also the names of non-screening-detected and outside screening). Some studies have shown that mortality among true attendees that suffered from breast cancer, invited to have a mammography, was reduced by 22%. Patient mortality was obviously reduced to 28% [9]. Survival benefits among

breast cancer patients using the screening-detected mode may be associated with biological differences related to estrogen (ER) and/or progesterone (PR) receptor status, Her2 status, and Ki67 index [10-13].

Recently, the mode of detection in breast cancer has become a hot topic of intensive research. Many retrospective articles have reported that the screening-detected mode was associated with better prognosis in patients with breast cancer, compared with other detection modes [10-22]. However, the results of other articles are inconclusive. No consensus has been reached. Some studies have reported that the screening-detected mode is prognostically irrelevant in breast cancer patients [7, 23, 24]. Therefore, it is worthwhile to further evaluate the prognostic and molecular subtypes of different detection modes in breast cancer. Accordingly, this study performed a systematic review and meta-analysis to evaluate the prognostic value of detection modes, exploring the association of molecular subtypes in breast cancer.

Material and methods

Search strategy and study selection

Eligible articles were exhaustively searched in PubMed, Embase, and Web of Science up through August 2018. Search strategies used the following terms: "breast cancer, breast carcinoma, breast tumor or breast neoplasm", "detection mode, screen-detected, symptomatically, interval, or outside screening", and "prognosis, survival, or outcome". All potential studies were reviewed. The most recent or largest sample size randomized controlled trials were selected when duplicated data were published.

Inclusion and exclusion criteria

Inclusion criteria were as follows: (1) Investigated the association between roles of detection mode (screen-detected, symptomatic, interval, and outside screening) and patient prognosis [overall survival (OS) and/or disease-free survival (DFS)]; (2) Patients that suffered from breast cancer, with a follow-up period of no less than 60 months; (3) Only English language studies were selected; and (4) The most recent report or most complete one was selected when the same author reported or duplicated data were published. Exclusion criteria were as follows: (1) Studies concerning animal experiments or basic research, with a theme irrelevant to breast cancer; (2) Studies failing to report data obtaining HR and 95% CI; (3) Duplicate reports and overlapping data; and (4) Published in a language with no English. Eligible randomized controlled trials were carefully examined by three authors. Aiming to reach a consensus, disagreements concerning conflicting outcomes were discussed between the three independent authors.

Data extraction and quality assessment

Included studies were carefully captured by three independent reviewers for possible inclusion. Any disagreements were resolved by discussion between the two reviewers or via consultation with a third reviewer. The following data were extracted from all candidate articles: name of first author, publication year, country, number of patients, age (years) or mean (standard deviation, SD) of patients, mode of detection and number of patients, survival analysis, HR for OS/DFS and 95% CI, and molecular subtypes in breast cancer. In this meta-analysis, survival dates of HR and 95% CIs were directly extracted from Kaplan-Meier survival curves of included articles, based on Tierney's methods [25]. Aiming to identify high-quality randomized controlled trials, each included study was scored according to the Newcastle-Ottawa Scale (NOS) [26]. Scores for this scale vary from 0-9. Studies with a score ≥6 are considered high quality. A consensus NOS score for each item was achieved via discussion between the three independent reviewers.

Statistical analysis

Statistical analyses were performed using Stata 12.0 software and Review Manager Version 5.3. Heterogeneity of individual HRs across eligible studies was estimated by Cochran's Q test and Higgin's I^2 test (a value of P less than 0.10 for the Q-test or/and I^2 more than 50% represents statistically significant heterogeneity) [27, 28]. A random-effects model or fixed-effects model was applied depending on heterogeneity analysis. The former indicates sig-

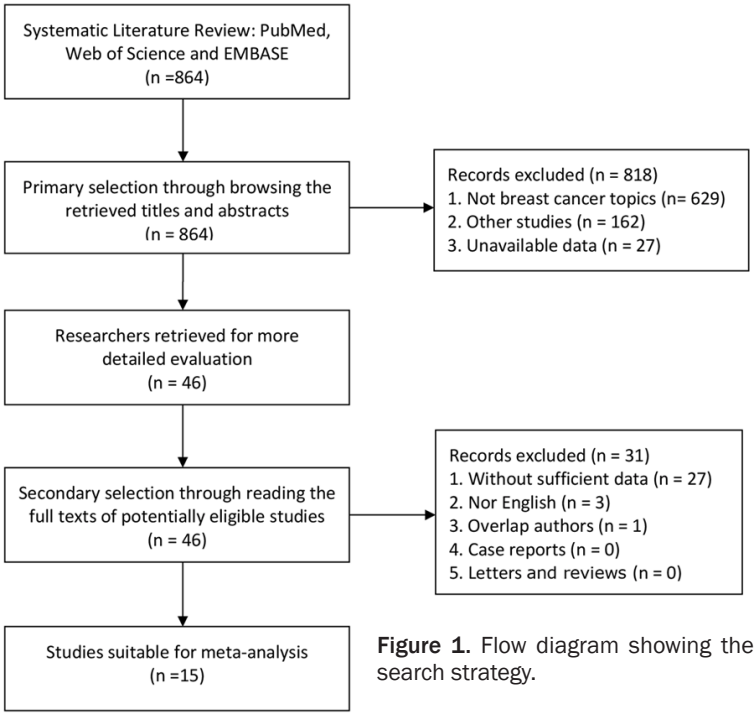

Figure 1. Flow diagram showing the search strategy.

nificant heterogeneity. HRs (95% CI) were extracted from the prognostic value of detection mode in breast cancer. Subgroup analysis was further applied to the interpretation of identified heterogeneity. Publication bias was calculated according to funnel plots with Begg's test. Generated *p* values<0.05 indicate significant bias. *P* values less than 0.05 indicate statistical significance.

Result

Study selection and characteristics

A flow diagram displays the search strategy, including a total of 15 randomized controlled trials. A total of 57,542 patients that suffered from breast cancer are considered in this meta-analysis (**Figure 1**). Main baseline characteristics of the 15 included studies are presented in **Table 1**. The search encompassed 10 countries (Sweden, Norway, China, Naples, Korea, Finland, United Kingdom, Singapore, America, and Canada) regarding literature published from 2004 to 2016. HRs and 95% CIs were reported directly from the original studies by Kaplan-Meier survival curves. As shown in **Table 2**, quality assessment of all eligible studies was performed by NOS. Most scores of these randomized controlled trials were 9 s, indicating that the methodological quality was relatively high and suitable for meta-analysis.

Meta-analysis

Association between the roles of detection mode and patient prognosis is shown in **Figures 2** and **3**. Results demonstrate that the mode of screening-detection was associated with good survival outcomes of breast cancer patients. Results suggest that combined HRs (HR = 2.78; 95% CI, 2.38-3.24, P<0.00001) of other detection methods are associated with poor survival, according to univariable analysis with a random-effects model among the 11 included studies (**Figure 2**). Results suggest that the combined HRs (HR = 1.60; 95% CI, 1.43-1.79, P< 0.00001) of other detection methods indicate worse survival, according to multivariable analysis with a random-effects model among the 14 included studies (**Figure 3**).

As shown in **Table 3**, correlation between detection method (screening detection method vs. other detection method) and molecular subtypes in breast cancer were explored in this meta-analysis (**Figure 4**). According to results of evidence synthesis, it was found that the screening-detection mode significantly correlated with ER positive (OR = 1.58, 95% CI [1.31, 1.91]) (**Figure 4A**), PR positive (OR = 1.43, 95% CI [1.33, 1.53]) (**Figure 4B**), HER2 positive (OR = 0.75, 95% CI [0.67, 0.83]) (**Figure 4C**), and Ki67 positive (OR = 0.57, 95% CI [0.45, 0.73]) (**Figure 4D**).

Due to heterogeneity, subgroup analyses were also conducted, as shown in **Table 4**. This was done by stratifying combined data according to analysis type (univariate vs. multivariate), number of patients (≤1000 vs. >1000), and ethnicity (Asian vs. Caucasian).

Publication bias

As shown in **Figure 5**, Begg's test, Egger's test, and funnel plots were performed to estima-

Table 1. Characteristics of included studies

References	Year	Country	Patient No.	Age (years)/Mean (SD) No.	Detection mode (patient) No.	Survival analysis	HR (95% CI)
Falck AK, et al.	2016	Sweden	434	Patients aged 45-74 years, 434	Screening No., 229 Symptomatic No., 205	Symptomatic (U, M) Screening (U) Screening (M)	1 [Reference] 0.5 (0.3-0.9) 0.7 (0.4-1.3)
Hofvind S, et al.	2015	Norway	8344	Screening, 60.1 (5.5) Interval, 59.6 (5.2) Outside screening, 57.7 (6.1)	Screening No., 4835 Interval No., 1644 Outside screening No., 1865	Screening (U, M) Interval (U) Outside screening (U) Interval (M) Outside screening (M)	1 [Reference] 4.4 (3.2-6.1) 4.9 (3.6-6.7) 2.1 (1.5-3.0) 2.6 (1.9-4.1)
Chuang SL, et al.	2014	China	2381	≥60 years, 1093 <60 years, 1288	Screening No., 1319 Clinically No., 1062	Clinically (U, M) Screening (U) Screening (M)	1 [Reference] 0.2 (0.1-0.3) 0.5 (0.3-0.7)
Crispo A, et al.	2013	Italy	448	≥50 years, 292 <50 years, 156	Screening No., 334 Symptomatic No., 114	Screening (M) Symptomatic (M)	1 [Reference] 2.7 (0.9-7.8)
Kim J, et al.	2012	Korea	3141	≥60 years, 407 <60 years, 2734	Screening No., 1025 Symptomatic No., 2116	Screening (M) Symptomatic (M)	1 [Reference] 1.2 (0.8-1.9)
Biesheuvel C, et al.	2011	Sweden	2470	≥60 years, 1409 <60 years, 1061	Screening No., 1546 Interval No., 521 Symptomatic No., 403	Screening (U, M) Interval (U) Symptomatic (U) Interval (M) Symptomatic (M)	1 [Reference] 3.0 (2.2-3.9) 3.6 (2.7-4.9) 1.4 (1.0-1.9) 1.6 (1.2-2.2)
Lehtimäki T, et al.	2011	Finland	1884	≥60 years, 871 <60 years, 1013	Screening No., 408 Outside screening No., 1476	Screening (M) Outside screening (M)	1 [Reference] 1.7 (1.1-2.7)
Nagtegaal ID, et al.	2011	UK	21382	Not available	Screening No. 9259, Interval No., 5413 Symptomatic No., 6710	Screening (U, M) Interval (U) Symptomatic (U) Interval (M) Symptomatic (M)	1 [Reference] 2.3 (2.1-) 3.4 (3.2-3.7) 1.3 (1.1-2.4) 1.5 (1.3-1.7)
Chuwa EW, et al.	2009	Singa-pore	767	Screening, 52.4 (8.7) Symptomatic, 54.2 (11.4)	Screening No., 103 Symptomatic No., 664	Screening (U) Symptomatic (U)	1 [Reference] 0.6 (0.1-3.0)
Dawson SJ, et al.	2009	UK	1379	≥60 years, 488 <60 years, 891	Screening No., 610 Not screening No., 769	Not screening (U, M) Screening (U) Screening (M)	1 [Reference] 0.4 (0.3-0.6) 0.4 (0.3-0.6)
Dong W, et al.	2008	America	5481	≥60 years, 1879 <60 years, 3602	Screening No., 2387 Symptomatic No., 3094	Screening (U, M) Symptomatic (U) Symptomatic (M)	1 [Reference] 2.40 (2.0-2.9) 1.3 (1.0-1.7)
Sihto H, et al.	2008	Finland	1236	≥60 years, 576 <60 years, 660	Screening No., 247 Not screening No., 989	Screening (M) Outside screening (M)	1 [Reference] 1.8 (1.1-2.8)
Wishart GC, et al.	2008	UK	5604	≥60 years, 2657 <60 years, 2947	Screening No., 2226 Symptomatic No., 3378	Symptomatic (U, M) Screening (U) Screening (M)	1 [Reference] 0.43 (0.3-0.5) 0.8 (0.6-1.0)
Shen Y, et al.	2005	Canada	608	Not available	Screening No. 132, Interval No., 94 Symptomatic No., 382	Screening (U, M) Interval (U) Symptomatic (U) Interval (M) Symptomatic (M)	1 [Reference] 2.1 (1.4-3.2) 2.2 (1.6-3.0) 1.6 (1.0-2.5) 1.4 (1.4-2.0)
Joensuu H, et al.	2004	Finland	1983	≥60 years, 902 <60 years, 1081	Screening No., 443 Outside screening No., 1540	Screening (U, M) Outside screening (U) Outside screening (M)	1 [Reference] 1.9 (1.2-3.1) 1.9 (1.1-3.3)

CI, confidence interval; HR, hazard ratio; M, multivariable analysis; No., number; SD, standard deviation; U, univariable analysis; UK, United Kingdom.

te publication bias. Funnel plots suggest that included studies had no evident asymmetry. Begg's funnel plots of publication bias suggest the mode of detection methods combined HRs for survival, according to univariate analysis (P = 0.767, **Figure 5A**) and multivariate analysis (P = 0.211, **Figure 5B**) among included studies. Findings suggest that significant publication bias did not exist in this meta-analysis.

Discussion

Present results suggest that survival of breast cancer is significantly better in patients using the screening-detection method than in patients using other detection methods (including symptomatic, interval, and outside screening methods). Previous studies have reported that patients suffering from breast cancer, detected

Table 2. Quality assessment of eligible studies with Newcastle-Ottawa scale

References	Year	Selection	Comparability	Outcome	NOS
Falck AK, et al.	2016	★★★★	★★	★★★	9
Hofvind S, et al.	2015	★★★★	★★	★★★	9
Chuang SL, et al.	2014	★★★★	★	★★★	8
Crispo A, et al.	2013	★★★★	★★	★★★	9
Kim J, et al.	2012	★★★★	★★	★★★	9
Biesheuvel C, et al.	2012	★★★★	★★	★★★	9
Lehtimäki T, et al.	2011	★★★★	★★	★★★	9
Nagtegaal ID, et al.	2011	★★★★	★★	★★★	9
Chuwa EW, et al.	2009	★★★★	★★	★★	8
Dawson SJ, et al.	2009	★★★★	★★	★★★	9
Dong W, et al.	2008	★★★★	★★	★★★	9
Sihto, et al.	2008	★★★★	★★	★★★	9
Wishart, et al.	2008	★★★★	★	★★★	8
Shen Y, et al.	2005	★★★★	★★	★★★	9
Joensuu H, et al.	2004	★★★★	★★	★★★	9

Comparability (Outcome not present at the start of the study, Control for Important factors); NOS, Newcastle-Ottawa Quality Assessment Scale; Outcome (Assessment of outcomes, Adequacy of follow-up, Length of follow-up); Selection (Representativeness of the exposed cohort, Selection unexposed cohort, Ascertainment of exposure).

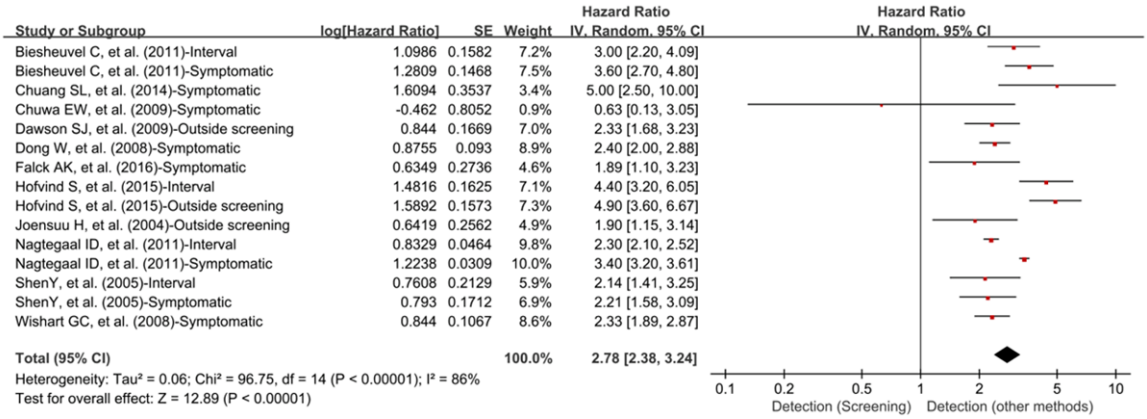

Figure 2. Forest plots concerning the association between the prognostic value of detection mode and survival in breast cancer, according to univariate analysis.

during screening mammography, had a lower risk of dying as a result of tumors than patients whose breast cancer was detected with outside screening. Results suggest significant survival differences between screening-detection and outside screening, according to post-diagnostic follow-ups of more than 10 years [13, 18]. Different detection methods in breast cancer show survival differences which cannot be explained by bias-related variables, such as clinical characteristics, histopathological, extent of disease, and molecular subtypes prognostic factors.

In past decades, researchers have been dedicated to obtaining the significance of a potential prognostic factor in breast cancer, aiming to identify new prognostic factors for better clinical decisions regarding therapy and outcomes. Many studies have indicated that the method of screening-detection was associated with good survival outcomes in breast cancer patients, considering it to be an independent prognostic factor [11, 22, 29, 30]. However, there has been consensus reached. Therefore, the current meta-analysis aimed to clarify the controversial issue for the first time.

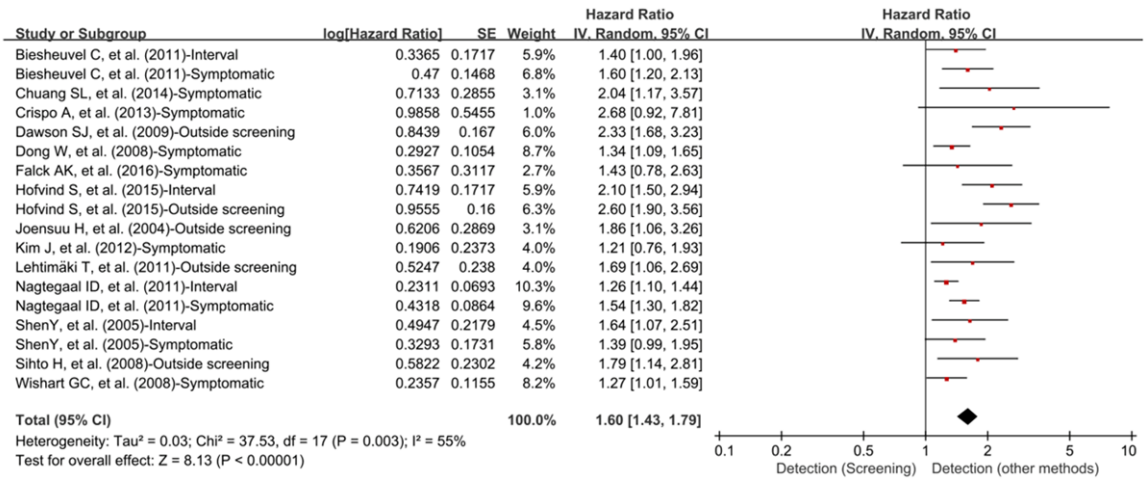

Figure 3. Forest plots concerning the association between the prognostic value of detection mode and survival in breast cancer, according to multivariate analysis.

Table 3. Association of detection mode (screening-detected vs. other detection mode) and risk of molecular in breast cancer

Molecular type	Number of studies	Number of patients	OR (95% CI)	*P*-value	Heterogeneity	
					I^2 (%)	*P*-value
ER status	11	16,785	1.58 (1.31-1.91)	<0.00001	77	<0.00001
PR status	11	16,706	1.43 (1.33-1.53)	<0.00001	35	0.12
HER2 status	7	11,143	0.75 (0.67-0.83)	<0.00001	32	0.18
Ki67 status	7	7,665	0.57 (0.45-0.73)	<0.00001	73	0.0009

CI, confidence interval; OR, odds ratio.

Results from evidence indicate that screening-detection could be regarded as an available prognostic factor, according to univariate analysis (pooled HR = 2.78; 95% CI, 2.38-3.24) and multivariate analysis (pooled HR = 1.60; 95% CI, 1.43-1.79) for survival among breast cancer patients. In patients diagnosed with breast cancer in the screen-detected group, the tumors tended to be smaller, more often with a lower histological grade, compared with tumors in the other detection group. Patients in symptomatic, interval, and outside screening groups tended to be older. Studies have suggested that the age of patients is an independent prognostic factor, with younger ages showing more aggressive tumor behavior in breast cancer [31]. Pooled analysis also revealed that screening-detection was significantly associated with higher expression of ER (pooled OR = 1.58; 95% CI, 1.31-1.91) and PR (pooled OR = 1.43; 95% CI, 1.33-1.53), while showing association with a lower risk of HER2 positive (pooled OR = 0.75; 95% CI, 0.67-0.83) and Ki67 index (pooled OR = 0.57; 95% CI, 0.45-0.73). In other words, the present meta-analysis suggests that screening-detected tumors are associated with St, Gallen luminal A-like subtype. These patients had a better prognosis, compared with other detection modes, in accord with previous findings [7, 32]. To understand the prognostic significance of detection methods in breast cancer, it is necessary to obtain a relatively large sample size of randomized controlled trials, conducting comprehensive evaluations by synthesizing and gathering as much valuable data as possible.

Although the results of pooled analysis are promising, there were several limitations. First, the quality of most included studies was relatively different. Second, the relatively high variability for different detection methods and published year may have contributed to inconsistent results within included studies. Third, some included studies were retrospective studies rather than randomized prospective studies.

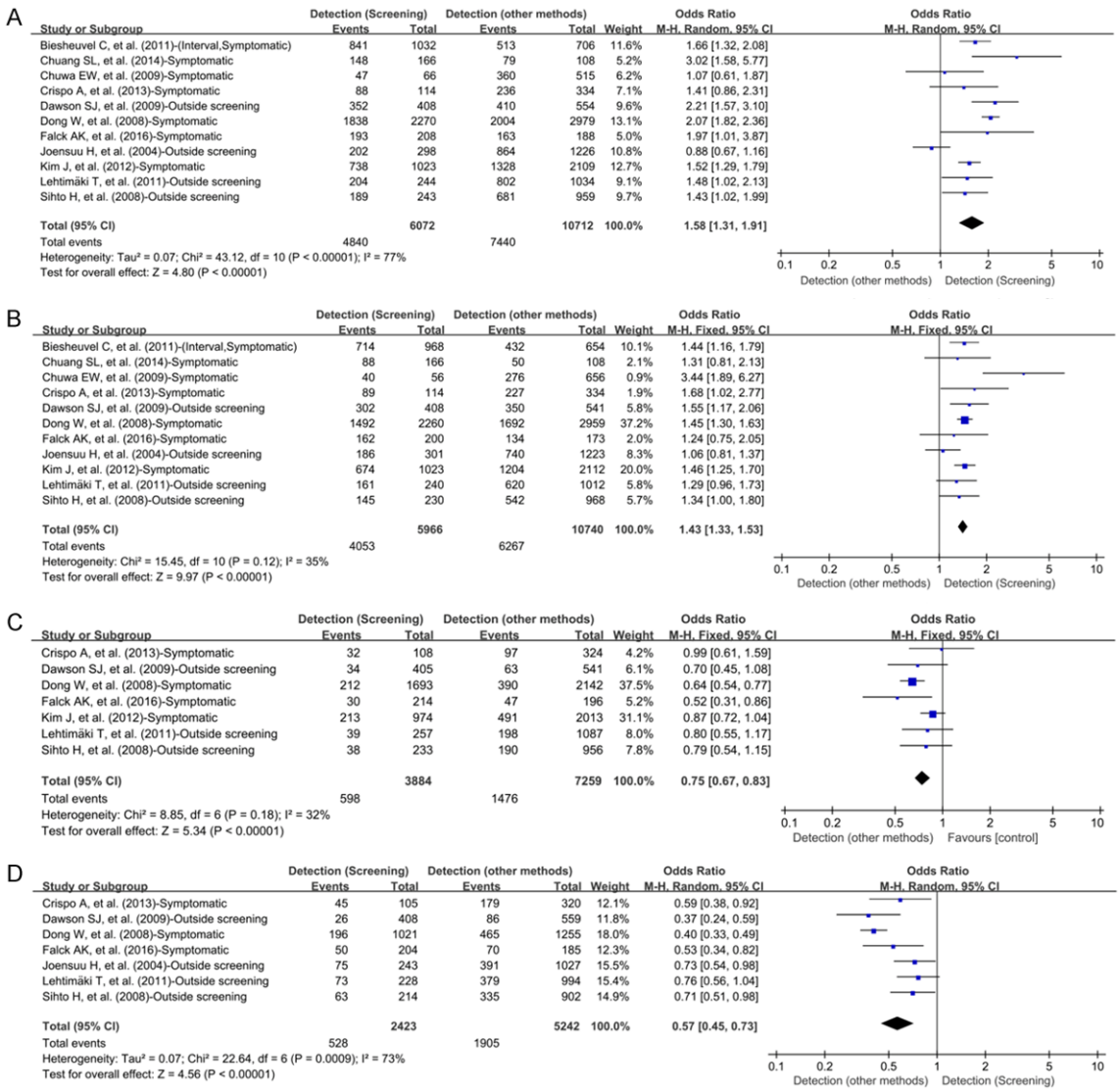

Figure 4. Forest plots of studies evaluating the association between the prognostic values of detection mode and molecular in breast cancer, according to a random-effects model or fixed-effects model. A. ER status (negative vs. positive), B. PR status (negative vs. positive), C. HER2 status (negative vs. positive) D. Ki67 status (negative vs. positive).

Therefore, more well-designed prospective studies, using stricter quality criteria, will contribute to further improving the reliability of pooled conclusions.

In conclusion, the present meta-analysis demonstrates that screening-detection can predict good prognosis, compared with other detection modes, in breast cancer patients. Results of this pooled analysis indicate that screen-detection patients were more likely to express ER and/or PR and show a lower HER2 and Ki67 index. However, more multicenter prospective studies are necessary to clarify the clinical relevance and provide a precise explanation for the roles of detection modes in breast cancer.

Disclosure of conflict of interest

None.

Address correspondence to: Weimin Zhou, Department of Vascular Surgery, The Second Affiliated Hospital of Nanchang University, No 1#, Minde Road, Nanchang 330006, Jiangxi Province, China. E-mail: drzwm@sina.com; Guobao Liu, Department of Radiology, The 908th Hospital of Chinese PLA Joint Logistic Support Force, Yingtan 335000, Jiangxi Province, China. E-mail: 392594238@qq.com

Table 4. Pooled HR for the roles of detection modes according to subgroup analysis

Analysis type	Patients	Ptudies	PHR (95% CI)	*P* value	I^2 (%)	*P* value
Univariate	50833	11	2.78 (2.38-3.24)	<0.00001	86%	<0.00001
Multivariate	56775	14	1.60 (1.43-1.79)	<0.00001	55%	0.003
No. of patients (Univariate)						
≤1000	1809	3	2.07 (1.64-2.61)	<0.00001	0%	0.048
>1000	49024	8	2.99 (2.52-3.55)	<0.00001	88%	<0.00001
No. of patients (Multivariate)						
≤1000	1490	3	1.52 (1.20-1.92)	0.0006	0%	0.68
>1000	55285	11	1.64 (1.43-1.89)	<0.00001	67%	0.0003
Ethnicity (Univariate)						
Asian	3148	2	2.01 (0.27-15.10)	0.50	82%	0.02
Caucasian	47685	9	2.76 (2.36-3.22)	<0.00001	87%	<0.00001
Ethnicity (Multivariate)						
Asian	5522	2	1.53 (0.92-2.55)	0.10	50%	0.16
Caucasian	51253	12	1.61 (1.43-1.81)	<0.00001	58%	0.002

CI, confidence interval; HR, hazard ratio; No. number.

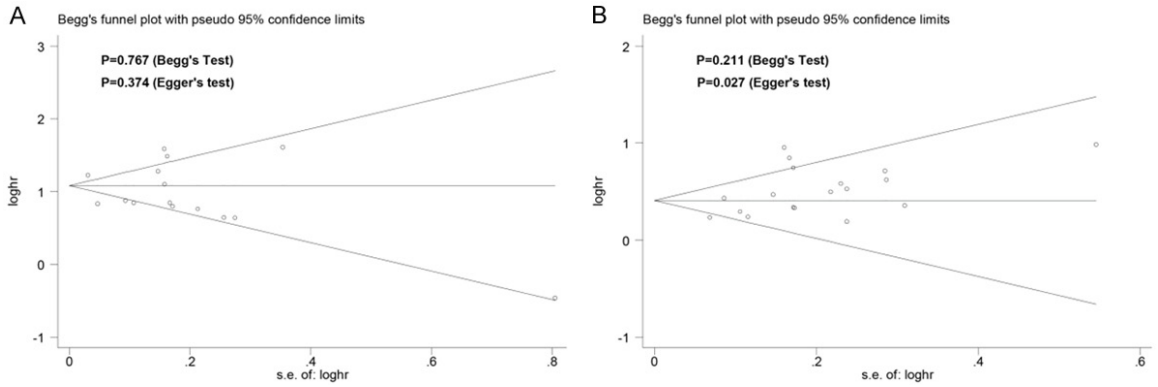

Figure 5. Summary of Begg's funnel plots of publication bias for survival in all patients with breast cancer. (A) univariate analysis; (B) multivariate analysis.

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