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

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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 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 cancerrelated 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 nonscreening-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 screeningdetected 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 diseasefree 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% Cl; (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  $\geq 6$  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<sup>2</sup> test (a value of *P* less than 0.10 for the Q-test or/and I<sup>2</sup> more than 50% represents statistically significant heterogeneity) [27, 28]. A random-effects model or fixedeffects model was applied depending on heterogeneity analysis. The former indicates sig-



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 screeningdetection 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 ( $\leq$ 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-

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)

Table 1. Characteristics of included stud	ies
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Cl, 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

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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

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

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).

			Hazard Ratio	Hazard Ratio
Study or Subgroup	log[Hazard Ratio] SE	Weight	IV. Random, 95% CI	IV. Random, 95% CI
Biesheuvel C, et al. (2011)-Interval	1.0986 0.1582	7.2%	3.00 [2.20, 4.09]	
Biesheuvel C, et al. (2011)-Symptomatic	1.2809 0.1468	7.5%	3.60 [2.70, 4.80]	
Chuang SL, et al. (2014)-Symptomatic	1.6094 0.3537	3.4%	5.00 [2.50, 10.00]	
Chuwa EW, et al. (2009)-Symptomatic	-0.462 0.8052	0.9%	0.63 [0.13, 3.05]	
Dawson SJ, et al. (2009)-Outside screening	0.844 0.1669	7.0%	2.33 [1.68, 3.23]	
Dong W, et al. (2008)-Symptomatic	0.8755 0.093	8.9%	2.40 [2.00, 2.88]	
Falck AK, et al. (2016)-Symptomatic	0.6349 0.2736	4.6%	1.89 [1.10, 3.23]	
Hofvind S, et al. (2015)-Interval	1.4816 0.1625	7.1%	4.40 [3.20, 6.05]	
Hofvind S, et al. (2015)-Outside screening	1.5892 0.1573	7.3%	4.90 [3.60, 6.67]	
Joensuu H, et al. (2004)-Outside screening	0.6419 0.2562	4.9%	1.90 [1.15, 3.14]	
Nagtegaal ID, et al. (2011)-Interval	0.8329 0.0464	9.8%	2.30 [2.10, 2.52]	-
Nagtegaal ID, et al. (2011)-Symptomatic	1.2238 0.0309	10.0%	3.40 [3.20, 3.61]	-
ShenY, et al. (2005)-Interval	0.7608 0.2129	5.9%	2.14 [1.41, 3.25]	
ShenY, et al. (2005)-Symptomatic	0.793 0.1712	6.9%	2.21 [1.58, 3.09]	
Wishart GC, et al. (2008)-Symptomatic	0.844 0.1067	8.6%	2.33 [1.89, 2.87]	
Total (95% CI)		100.0%	2.78 [2.38, 3.24]	◆
Heterogeneity: Tau <sup>2</sup> = 0.06; Chi <sup>2</sup> = 96.75, df =	14 (P < 0.00001); I <sup>2</sup> = 86%			
Test for overall effect: Z = 12.89 (P < 0.00001)	)			0.1 0.2 0.5 1 2 5 10 Detection (Screening) Detection (other methods)

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.

Study or Subgroup         log[Hazard Ratio]         SE         Weight         IV. Random. 95% Cl         IV. Random. 95% Cl           Biesheuvel C, et al. (2011)-Interval         0.3365         0.1717         5.9%         1.40 [1.00, 1.96]           Biesheuvel C, et al. (2011)-Symptomatic         0.47         0.1468         6.8%         1.60 [1.20, 2.13]           Chuang SL, et al. (2014)-Symptomatic         0.713         0.2855         3.1%         2.04 [1.17, 3.57]
Biesheuvel C, et al. (2011)-Interval         0.3365         0.1717         5.9%         1.40 [1.00, 1.96]           Biesheuvel C, et al. (2011)-Symptomatic         0.47         0.1468         6.8%         1.60 [1.20, 2.13]           Chuang SL, et al. (2014)-Symptomatic         0.713         0.2855         3.1%         2.04 [1.17, 3.57]
Biesheuvel C, et al. (2011)-Symptomatic         0.47         0.1468         6.8%         1.60 [1.20, 2.13]           Chuang SL, et al. (2014)-Symptomatic         0.7133         0.2855         3.1%         2.04 [1.17, 3.57]
Chuang SL, et al. (2014)-Symptomatic 0.7133 0.2855 3.1% 2.04 [1.17, 3.57]
Crispo A, et al. (2013)-Symptomatic 0.9858 0.5455 1.0% 2.68 [0.92, 7.81]
Dawson SJ, et al. (2009)-Outside screening 0.8439 0.167 6.0% 2.33 [1.68, 3.23]
Dong W, et al. (2008)-Symptomatic 0.2927 0.1054 8.7% 1.34 [1.09, 1.65]
Falck AK, et al. (2016)-Symptomatic         0.3567         0.3117         2.7%         1.43 [0.78, 2.63]
Hofvind S, et al. (2015)-Interval 0.7419 0.1717 5.9% 2.10 [1.50, 2.94]
Hofvind S, et al. (2015)-Outside screening 0.9555 0.16 6.3% 2.60 [1.90, 3.56]
Joensuu H, et al. (2004)-Outside screening 0.6206 0.2869 3.1% 1.86 [1.06, 3.26]
Kim J, et al. (2012)-Symptomatic 0.1906 0.2373 4.0% 1.21 [0.76, 1.93]
Lehtimäki T, et al. (2011)-Outside screening 0.5247 0.238 4.0% 1.69 [1.06, 2.69]
Nagtegaal ID, et al. (2011)-Interval 0.2311 0.0693 10.3% 1.26 [1.10, 1.44]
Nagtegaal ID, et al. (2011)-Symptomatic 0.4318 0.0864 9.6% 1.54 [1.30, 1.82]
ShenY, et al. (2005)-Interval         0.4947         0.2179         4.5%         1.64 [1.07, 2.51]
ShenY, et al. (2005)-Symptomatic 0.3293 0.1731 5.8% 1.39 [0.99, 1.95]
Sihto H, et al. (2008)-Outside screening 0.5822 0.2302 4.2% 1.79 [1.14, 2.81]
Wishart GC, et al. (2008)-Symptomatic         0.2357         0.1155         8.2%         1.27 [1.01, 1.59]
Total (95% Cl) 100.0% 1.60 [1.43, 1.79]
Heterogeneity: Tau <sup>2</sup> = 0.03; Chi <sup>2</sup> = 37.53, df = 17 (P = 0.003); l <sup>2</sup> = 55%
Test for overall effect: Z = 8.13 (P < 0.00001) Detection (Screening) Detection (Screening) Detection (Screening)

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

Malagulartypa	Number of studios	Number of potiente		Dvoluo	Heterogeneity		
Molecular type	Number of Studies	Number of patients	UR (95% CI)	P-value	l² (%)	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 screeningdetection could be regarded as an available prognostic factor, according to univariate analysis (pooled HR = 2.78; 95% Cl, 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% Cl. 1.33-1.53), while showing association with a lower risk of HER2 positive (pooled OR = 0.75; 95% Cl, 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.

Α		Detection (Screening)		Detection (other methods)		Odds Ratio		Odds Ratio		
Λ.	Study or Subgroup	Events	Total	Events	Total	Weight	M-H. Random, 95% C	M-H. Random, 95% Cl		
	Biesheuvel C, et al. (2011)-(Interval,Symptomatic	) 841	1032	513	706	11.6%	1.66 [1.32, 2.08]			
	Chuang SL, et al. (2014)-Symptomatic	148	166	79	108	5.2%	3.02 [1.58, 5.77]			
	Chuwa EW, et al. (2009)-Symptomatic	47	66	360	515	6.2%	1.07 [0.61, 1.87]	-		
	Crispo A, et al. (2013)-Symptomatic	88	114	236	334	7.1%	1.41 [0.86, 2.31]			
	Dawson SJ, et al. (2009)-Outside screening	352	408	410	554	9.6%	2.21 [1.57, 3.10]			
	Dong W, et al. (2008)-Symptomatic	1838	2270	2004	2979	13.1%	2.07 [1.82, 2.36]			
	Falck AK, et al. (2016)-Symptomatic	193	208	163	188	5.0%	1.97 [1.01, 3.87]			
	Joensuu H, et al. (2004)-Outside screening	202	298	864	1226	10.8%	0.88 [0.67, 1.16]			
	Kim J, et al. (2012)-Symptomatic	738	1023	1328	2109	12.7%	1.52 [1.29, 1.79]			
	Sibte H et al. (2008) Outside screening	204	244	602	1034	9.1%	1.40 [1.02, 2.13]			
	Sinto H, et al. (2008)-Outside screening	189	243	661	929	9.7%	1.43 [1.02, 1.99]			
	Total (95% CI)		6072		10712	100.0%	1.58 [1.31, 1.91]	•		
	Total events	4840	0012	7440	10112	100.070		-		
	Heterogeneity: $Tau^2 = 0.07$ : $Chi^2 = 43.12$ , $df = 10$	(P < 0.00001): l <sup>2</sup> =	77%	7440				+ + + + + + + + + + + + + + + + + + + +	+	
	Test for overall effect: $Z = 4.80$ (P < 0.00001)	(1 - 0.00001), 1 -						0.1 0.2 0.5 1 2 5	10	
								Detection (other methods) Detection (Screening)		
B		Detection (S	creening)	Detection (other	r methods)		Odds Ratio	Odds Ratio		
Ξ.	Study or Subgroup	Events	Tota	Events	Tota	I Weight	M-H, Fixed, 95% CI	M-H. Fixed, 95% CI		
	Biesheuvel C, et al. (2011)-(Interval,Symptomatic	c) 714	968	3 432	654	10.1%	1.44 [1.16, 1.79]			
	Chuang SL, et al. (2014)-Symptomatic	88	166	5 50	108	3 2.1%	1.31 [0.81, 2.13]			
	Chuwa EW, et al. (2009)-Symptomatic	40	56	3 276	656	5 0.9%	3.44 [1.89, 6.27]			
	Crispo A, et al. (2013)-Symptomatic	89	114	227	334	1.9%	1.68 [1.02, 2.77]			
	Dawson SJ, et al. (2009)-Outside screening	302	408	3 350	541	5.8%	1.55 [1.17, 2.06]			
	Dong W, et al. (2008)-Symptomatic	1492	2260	) 1692	2959	37.2%	1.45 [1.30, 1.63]			
	Falck AK, et al. (2016)-Symptomatic	162	200	) 134	173	3 2.0%	1.24 [0.75, 2.05]			
	Joensuu H, et al. (2004)-Outside screening	186	301	740	1223	8.3%	1.06 [0.81, 1.37]			
	Kim J, et al. (2012)-Symptomatic	674	1023	3 1204	2112	2 20.0%	1.46 [1.25, 1.70]			
	Lehtimäki T, et al. (2011)-Outside screening	161	240	620	1012	2 5.8%	1.29 [0.96, 1.73]			
	Sihto H, et al. (2008)-Outside screening	145	230	542	968	5.7%	1.34 [1.00, 1.80]			
	Total (95% CI)		5966		10740	100.0%	1.43 [1.33, 1.53]	•		
	Total events	4053		6267						
	Heterogeneity: Chi <sup>2</sup> = 15.45, df = 10 (P = 0.12); I	² = 35%						01 02 05 1 2 5	10	
	Test for overall effect: Z = 9.97 (P < 0.00001)							Detection (other methods) Detection (Screening)	10	
0		Detection (Scr	enina)	Detection (other			Odds Ratio	Odds Ratio		
U		Deteonon (oon		Dotootion (other	methods)			oudo rutto		
	Study or Subgroup	Events	Total	Events	methods) Total	Weight	t M-H. Fixed, 95% C	M-H. Fixed, 95% Cl		
	Study or Subgroup	Events 32	Total	Events	methods) Tota 324	Weight	M-H. Fixed, 95% C	CI M-H. Fixed. 95% CI		
	Study or Subgroup Crispo A, et al. (2013)-Symptomatic	Events 32	<u>Total</u> 108	Events 97	methods) Tota 324	4.2%	M-H. Fixed, 95% C	CI M-H. Fixed. 95% CI		
	Study or Subgroup Crispo A, et al. (2013)-Symptomatic Dawson SJ, et al. (2009)-Outside screening Doog W, et al. (2009)-Symptomatic	Events 32 34 212	Total 108 405	Events 97 63	methods) <u>Tota</u> 324 541 2142	4.2%	M-H, Fixed, 95% C 0.99 [0.61, 1.59] 0.70 [0.45, 1.08]	CI M-H. Fixed. 95% CI		
	Study or Subgroup Crispo A, et al. (2013)-Symptomatic Dawson SJ, et al. (2009)-Outside screening Dong W, et al. (2008)-Symptomatic	Events 32 34 212	Total 108 405 1693	Events 97 63 390	methods) Tota 324 541 2142	4.2% 6.1%	M-H. Fixed. 95% C 0.99 [0.61, 1.59] 0.70 [0.45, 1.08] 0.64 [0.54, 0.74]			
	Study or Subgroup Crispo A, et al. (2013)-Symptomatic Dawson SJ, et al. (2009)-Outside screening Dong W, et al. (2008)-Symptomatic Falck AK, et al. (2016)-Symptomatic	Events 32 34 212 30	Total 108 405 1693 214	Events 97 63 390 47	methods) Total 324 541 2142 196	4.2% 6.1% 37.5% 5.2%	M-H. Fixed. 95% C           0.99 [0.61, 1.59]           0.70 [0.45, 1.08]           0.64 [0.54, 0.77]           0.52 [0.31, 0.86]           0.52 [0.31, 0.86]	Cl M-H. Fixed. 95% Cl		
	Study or Subgroup Crispo A, et al. (2013)-Symptomatic Dawson SJ, et al. (2009)-Outside screening Dong W, et al. (2008)-Symptomatic Falck AK, et al. (2016)-Symptomatic Kim J, et al. (2012)-Symptomatic	Events 32 34 212 30 213 20	Total 108 405 1693 214 974	Events 97 63 390 47 491	methods) Total 324 541 2142 196 2013	Weight 4.2% 6.1% 37.5% 5.2% 31.1%	M-H. Fixed, 95% C 9 0.99 [0.61, 1.59] 0.70 [0.45, 1.08] 0.64 [0.54, 0.77] 0.52 [0.31, 0.86] 0.87 [0.72, 1.04]	2 M-H_Fixed. 95% Cl		
	Study or Subgroup Crispo A, et al. (2013)-Symptomatic Dawson SJ, et al. (2009)-Outside screening Dong W, et al. (2008)-Symptomatic Falck AK, et al. (2016)-Symptomatic Kim J, et al. (2012)-Symptomatic Lehtmäki T, et al. (2011)-Outside screening	Events 32 34 212 30 213 39 20	Total 108 405 1693 214 974 257	Events 97 63 390 47 491 198	methods) Tota 324 541 2142 196 2013 1087	Weight 4.2% 6.1% 37.5% 5.2% 31.1% 8.0%	M-H. Fixed. 95% C           0.99 [0.61, 1.59]           0.70 [0.45, 1.08]           0.64 [0.54, 0.77]           0.52 [0.31, 0.86]           0.87 [0.72, 1.04]           0.80 [0.55, 1.17]	Cl M-H, Fixed, 95% Cl		
	Study or Subgroup Crispo A, et al. (2013)-Symptomatic Dawson SJ, et al. (2009)-Outside screening Dong W, et al. (2008)-Symptomatic Falck AK, et al. (2016)-Symptomatic Kim J, et al. (2017)-Symptomatic Lehtimäki T, et al. (2017)-Outside screening Sihto H, et al. (2008)-Outside screening	Events 32 34 212 30 213 39 38	Total 108 405 1693 214 974 257 233	Events 97 63 390 47 491 198 190	methods) Total 324 541 2142 196 2013 1087 956	Weight 4.2% 6.1% 37.5% 5.2% 31.1% 8.0% 7.8%	M-H. Fixed, 95% C           0.99 [0.61, 1.59]           0.70 [0.45, 1.08]           0.64 [0.54, 0.77]           0.52 [0.31, 0.86]           0.87 [0.72, 1.04]           0.80 [0.55, 1.17]           0.79 [0.54, 1.15]	Cl M-H-Fixed. 95% Cl		
	Study or Subgroup Crispo A, et al. (2013)-Symptomatic Dawson SJ, et al. (2009)-Outside screening Dong W, et al. (2009)-Symptomatic Falck AK, et al. (2016)-Symptomatic Kim J, et al. (2012)-Symptomatic Lehtimäki T, et al. (2011)-Outside screening Sihto H, et al. (2008)-Outside screening	Events 32 34 212 30 213 39 38	Total 108 405 1693 214 974 257 233	Events 97 63 390 47 491 198 190	methods) <u>Total</u> 324 541 2142 196 2013 1087 956 7250	Weight 4.2% 6.1% 37.5% 5.2% 31.1% 8.0% 7.8%	M-H. Fixed, 95% C           0.99 [0.61, 1.59]           0.70 [0.45, 1.08]           0.64 [0.54, 0.77]           0.52 [0.31, 0.86]           0.87 [0.72, 1.04]           0.80 [0.55, 1.17]           0.79 [0.54, 1.15]           0.79 [0.54, 1.15]	Cl M-H, Fixed, 95% Cl		
	Study or Subgroup Crispo A, et al. (2013)-Symptomatic Dawson SJ, et al. (2009)-Outside screening Dong W, et al. (2008)-Symptomatic Falck AK, et al. (2016)-Symptomatic Kim J, et al. (2012)-Symptomatic Lehtimäki T, et al. (2012)-Outside screening Sihto H, et al. (2008)-Outside screening Total (95% CI)	Events 32 34 212 30 213 39 38	Total 108 405 1693 214 974 257 233 3884	Events 97 63 390 47 491 198 190	methods) <u>Total</u> 324 541 2142 196 2013 1087 956 7259	Weight 4.2% 6.1% 37.5% 5.2% 31.1% 8.0% 7.8% 100.0%	M-H, Fixed, 95% C           0.99 [0.61, 1.59]           0.70 [0.45, 1.08]           0.64 [0.54, 0.77]           0.52 [0.31, 0.86]           0.87 [0.72, 1.04]           0.80 [0.55, 1.17]           0.79 [0.54, 1.15]           0.75 [0.67, 0.83]	A M-H, Fixed, 95% Cl		
	Study or Subgroup Crispo A, et al. (2013)-Symptomatic Dawson SJ, et al. (2009)-Outside screening Dong W, et al. (2006)-Symptomatic Falck AK, et al. (2016)-Symptomatic Kim J, et al. (2012)-Symptomatic Lehtimäki T, et al. (2013)-Outside screening Sihto H, et al. (2008)-Outside screening Total (95% CI) Total events	Events 32 34 212 30 213 39 38 598	Total 108 405 1693 214 974 257 233 3884	Events 97 63 390 47 491 198 190 1476	methods) Total 324 541 2142 196 2013 1087 956 7259	Weight 4.2% 6.1% 37.5% 5.2% 31.1% 8.0% 7.8% 100.0%	M-H, Fixed, 95% C           0.99 [0.61, 1.59]           0.70 [0.45, 1.08]           0.64 [0.54, 0.77]           0.52 [0.31, 0.86]           0.87 [0.72, 1.04]           0.80 [0.55, 1.17]           0.75 [0.67, 0.83]	M-H.Fixed. 95% Cl		
	Study or Subgroup Crispo A, et al. (2013)-Symptomatic Dawson SJ, et al. (2009)-Outside screening Dong W, et al. (2008)-Symptomatic Faick AK, et al. (2016)-Symptomatic Kim J, et al. (2012)-Symptomatic Lehtimäki T, et al. (2011)-Outside screening Sihto H, et al. (2008)-Outside screening Total (95% CI) Total events Heterogeneity: Chi <sup>p</sup> = 8.85, df = 6 (P = 0.18); I	Events         32           34         212           30         213           39         38           598         2           232         32%	Total           108           405           1693           214           974           257           233           3884	Events 97 63 390 47 491 198 190 1476	methods) <u>Total</u> 324 541 2142 196 2013 1087 956 7259	Weight 4.2% 6.1% 37.5% 5.2% 31.1% 8.0% 7.8% 100.0%	M-H, Fixed, 95% C           0.99 [0.61, 1.59]           0.70 [0.45, 1.08]           0.76 [0.45, 1.08]           0.64 [0.54, 0.77]           0.52 [0.31, 0.86]           0.87 [0.72, 1.04]           0.80 [0.57, 1.07]           0.75 [0.67, 0.83]	M-H.Fixed. 95% Cl	+ 10	
	Study or Subgroup Crispo A, et al. (2013)-Symptomatic Dawson SJ, et al. (2009)-Outside screening Dong W, et al. (2008)-Symptomatic Falck AK, et al. (2016)-Symptomatic Lehtimäki T, et al. (2017)-Outside screening Sihto H, et al. (2012)-Outside screening Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 8.85, df = 6 (P = 0.18); I Test for overall effect: Z = 5.34 (P < 0.00001)	Events 32 34 212 30 213 39 38 38 598 2° = 32%	Total           108           405           1693           214           974           257           233           3884	Events 97 63 390 47 491 198 190 1476	methods) Total 324 541 2142 196 2013 1087 956 7259	Weight 4.2% 6.1% 37.5% 5.2% 31.1% 8.0% 7.8%	M-H, Fixed, 95% C           0.99 [0.61, 1.59]           0.70 [0.45, 1.08]           0.64 [0.54, 0.77]           0.52 [0.31, 0.86]           0.87 [0.72, 1.04]           0.80 [0.55, 1.17]           0.79 [0.54, 1.15]           0.75 [0.67, 0.83]	M-H. Fixed. 95% Cl	+ 10	
	Study or Subgroup Crispo A, et al. (2013)-Symptomatic Dawson SJ, et al. (2009)-Outside screening Dong W, et al. (2008)-Symptomatic Falck AK, et al. (2016)-Symptomatic Kim J, et al. (2012)-Symptomatic Lehtimäki T, et al. (2012)-Outside screening Sihto H, et al. (2008)-Outside screening Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 8.85, df = 6 (P = 0.18); I Test for overall effect: Z = 5.34 (P < 0.00001)	Events 32 34 212 30 213 39 38 598 2 = 32%	Total 108 405 1693 214 974 257 233 3884	Events 97 63 390 47 491 198 190 1476	methods) Total 324 541 2142 196 2013 1087 956 7259	Weight 4.2% 6.1% 37.5% 5.2% 31.1% 8.0% 7.8%	M-H, Fixed, 95% C           0.99 [0.61, 1.59]           0.70 [0.45, 1.08]           0.75 [0.45, 1.08]           0.64 [0.54, 0.77]           0.52 [0.31, 0.86]           0.87 [0.72, 1.04]           0.80 [0.55, 1.17]           0.79 [0.54, 1.15]           0.75 [0.67, 0.83]	M-H.Fixed. 95% Cl	+ 10	
D	Study or Subgroup Crispo A, et al. (2013)-Symptomatic Dawson SJ, et al. (2009)-Outside screening Dong W, et al. (2008)-Symptomatic Falck AK, et al. (2016)-Symptomatic Lehtimäki T, et al. (2017)-Outside screening Sihto H, et al. (2012)-Outside screening Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 8.85, df = 6 (P = 0.18); I Test for overall effect: Z = 5.34 (P < 0.00001)	Events 32 34 212 30 213 39 38 2 = 32% 598 2 = 32%	Total 108 405 1693 214 974 257 233 3884	Events 97 63 390 47 491 198 190 1476 tection (other met	methods) <u>Total</u> 3242 541 2142 196 2013 1087 956 <b>7259</b> hods)	Weight 4.2% 6.1% 37.5% 5.2% 31.1% 8.0% 7.8%	M-H, Fixed, 95% C           0.99 [0.61, 1.59]           0.70 [0.45, 1.08]           0.64 [0.54, 0.07]           0.52 [0.31, 0.86]           0.87 [0.72, 1.04]           0.80 [0.55, 1.17]           0.75 [0.67, 0.83]           Odds Ratio	M-H. Fixed. 95% Cl	+ 10	
D	Study or Subgroup Crispo A, et al. (2013)-Symptomatic Dawson SJ, et al. (2009)-Outside screening Dong W, et al. (2009)-Symptomatic Falck AK, et al. (2016)-Symptomatic Kim J, et al. (2012)-Symptomatic Lehtimäki T, et al. (2011)-Outside screening Sihto H, et al. (2008)-Outside screening Total (95% CI) Total events Heterogeneity: Chi <sup>p</sup> = 8.85, df = 6 (P = 0.18); I Test for overall effect: Z = 5.34 (P < 0.00001) Study or Subgroup	Events 32 34 212 30 213 39 38 2= 32% 2= 32%	Total 108 405 1693 214 974 257 233 3884 sing) De Total	Events 97 63 390 47 491 198 190 1476 tection (other met	methods) <u>Total</u> 324 541 2142 196 2013 1087 956 7259 hods) <u>Total W</u>	Weight 4.2% 6.1% 37.5% 5.2% 31.1% 8.0% 7.8% 100.0%	M-H, Fixed, 95% C           0.99 [0.61, 1.59]           0.70 [0.45, 1.08]           0.64 [0.54, 0.78]           0.65 [0.54, 0.77]           0.52 [0.31, 0.86]           0.87 [0.72, 1.04]           0.80 [0.55, 1.17]           0.79 [0.54, 1.15]           0.75 [0.67, 0.83]           Odds Ratio	M-H. Fixed. 95% Cl	+ 10	
D	Study or Subgroup Crispo A, et al. (2013)-Symptomatic Dawson SJ, et al. (2009)-Outside screening Dong W, et al. (2008)-Symptomatic Falck AK, et al. (2016)-Symptomatic Kim J, et al. (2012)-Symptomatic Lehtmäki T, et al. (2011)-Outside screening Sihto H, et al. (2008)-Outside screening Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 8.85, df = 6 (P = 0.18); I Test for overall effect: Z = 5.34 (P < 0.00001) Study or Subgroup Crispo A, et al. (2013)-Symptomatic	Events 32 34 212 30 213 39 38 <sup>598</sup> <sup>2</sup> = 32% Detection (Screent Events 45	Total 108 405 1693 214 974 257 233 3884 ing) De Total 105	Events 97 63 390 47 491 198 190 1476 tection (other met <u>Events</u> 179	methods) <u>Total</u> 324 541 2142 196 2013 1087 956 7259 hods) <u>Total W</u> 320 1	Weight 4.2% 6.1% 37.5% 5.2% 31.1% 8.31.1% 100.0% eight M 2.1%	M-H, Fixed, 95% C           0.99 [0.61, 1.59]           0.70 [0.45, 1.08]           0.64 [0.54, 0.77]           0.52 [0.31, 0.86]           0.87 [0.72, 1.04]           0.80 [0.55, 1.17]           0.75 [0.67, 0.83]           Odds Ratio           UHL Random, 95% CI           0.59 [0.8.0, 02]	2. M-H. Fixed. 95% Cl 	+ 10	
D	Study or Subgroup Crispo A, et al. (2013)-Symptomatic Dawson SJ, et al. (2009)-Outside screening Dong W, et al. (2008)-Symptomatic Falck AK, et al. (2016)-Symptomatic Lehtimäki T, et al. (2017)-Outside screening Sihto H, et al. (2012)-Outside screening Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 8.85, df = 6 (P = 0.18); I Test for overall effect: Z = 5.34 (P < 0.00001) Study or Subgroup Crispo A, et al. (2013)-Symptomatic Dawson SJ, et al. (2003)-Outside screenina	Events 32 34 212 30 213 39 38 <sup>2</sup> = 32% Detection (Screer <u>Events</u> 45 26	Total 108 405 1693 214 974 257 233 3884 ing) De Total 105 408	Events 97 63 390 47 491 198 190 1476 tection (other met <u>Events</u> 179 86	methods) <u>Total</u> 324 541 2142 196 2013 1087 956 7259 hods) <u>Total W</u> 320 1 559 1	Weight           4.2%           6.1%           37.5%           5.2%           31.1%           8.0%           7.8%           100.0%           eight         M           2.1%           1.8%	M-H, Fixed, 95% C           0.99 [0.61, 1.59]           0.70 [0.45, 1.08]           0.64 [0.54, 0.70]           0.52 [0.51]           0.64 [0.54, 0.77]           0.52 [0.51]           0.65 [0.55, 1.17]           0.75 [0.67, 0.83]           Odds Ratio           UH, Random, 95% CI           0.59 [0.38, 0.82]           0.37 [0.24, 0.59]	M-H. Fixed. 95% Cl M-H. Fixed. 95% Cl 0.1 0.2 0.5 1 2 5 Detection (other method) Favours [control] Odds Ratio M-H. Random. 95% Cl	+ 10	
D	Study or Subgroup Crispo A, et al. (2013)-Symptomatic Dawson SJ, et al. (2009)-Outside screening Dong W, et al. (2008)-Symptomatic Falck AK, et al. (2016)-Symptomatic Kim J, et al. (2012)-Symptomatic Lehtimäki T, et al. (2012)-Outside screening Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 8.85, df = 6 (P = 0.18); I Test for overall effect: Z = 5.34 (P < 0.00001) Study or Subgroup Crispo A, et al. (2009)-Outside screening Dong W, et al. (2009)-Outside screening	Events 32 34 212 30 213 39 38 598 598 2° = 32% Detection (Screen <u>Events</u> 45 26 196	Total 108 405 1693 214 974 257 233 3884 ing) De Total 105 408 1021	Events 97 63 390 47 491 198 190 1476 Events 179 86 465	methods) Total 324 541 2142 196 2013 1087 956 7259 hods) <u>Total W</u> 320 1 559 1 1255 1	Weight           4.2%           6.1%           37.5%           37.5%           31.1%           8.0%           100.0%           eight           2.1%           1.8%           8.0%	M-H, Fixed, 95% C           0.99 [0.61, 1.59]           0.70 [0.45, 1.08]           0.70 [0.45, 1.08]           0.64 [0.54, 0.77]           0.52 [0.31, 0.86]           0.87 [0.72, 1.04]           0.80 [0.55, 1.17]           0.75 [0.67, 0.83]           0.75 [0.67, 0.83]           Odds Ratio           LH, Random, 95% CI           0.59 [0.38, 0.92]           0.37 [0.24, 0.59]           0.40 [0.33, 0.49]	2. M-H, Fixed, 95% Cl 	+ 10	
D	Study or Subgroup Crispo A, et al. (2013)-Symptomatic Dawson SJ, et al. (2009)-Outside screening Dong W, et al. (2008)-Symptomatic Falck AK, et al. (2016)-Symptomatic Lehtimäki T, et al. (2017)-Outside screening Sihto H, et al. (2012)-Outside screening Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 8.85, df = 6 (P = 0.18); I Test for overall effect: Z = 5.34 (P < 0.00001) Study or Subgroup Crispo A, et al. (2016)-Symptomatic Dawson SJ, et al. (2016)-Symptomatic Dawson SJ, et al. (2016)-Symptomatic Dawson SJ, et al. (2016)-Symptomatic Dong W, et al. (2016)-Symptomatic	Events 32 34 212 30 213 39 38 598 ° = 32% Detection (Screet Events 45 26 196 50	Total 108 405 1693 214 974 257 233 3884 ing) De Total 105 408 1021 204	Events 97 63 390 47 491 198 190 1476 tection (other met <u>Events</u> 179 86 465 70	hods) Total 324 541 2142 196 2013 1087 956 7259 hods) <u>Total W</u> 320 1 559 1 1255 1 1255 1 1255 1	Weight           4.2%           6.1%           37.5%           37.5%           31.1%           8.0%           100.0%           eight           4.2%           1.8%           8.0%	M-H, Fixed, 95% C           0.99 [0.61, 1.59]           0.70 [0.45, 1.08]           0.76 [0.45, 1.08]           0.64 [0.54, 0.77]           0.52 [0.31, 0.86]           0.87 [0.72, 1.04]           0.80 [0.55, 1.17]           0.75 [0.67, 0.83]           0.75 [0.67, 0.83]           0.75 [0.67, 0.83]           0.37 [0.24, 0.59]           0.37 [0.24, 0.59]           0.40 [0.33, 0.49]           0.51 [0.44, 0.82]	All H-H Fixed, 95% Cl M-H. Fixed, 95% Cl 0.1 0.2 0.5 1 2 5 Detection (other methods) Favours [control] Odds Ratio M-H. Random, 95% Cl	+ 10	
D	Study or Subgroup Crispo A, et al. (2013)-Symptomatic Dawson SJ, et al. (2009)-Outside screening Dong W, et al. (2008)-Symptomatic Falck AK, et al. (2016)-Symptomatic Lehtimäki T, et al. (2015)-Symptomatic Lehtimäki T, et al. (2015)-Outside screening Total (95% CI) Total events Heterogeneiity: Chi <sup>2</sup> = 8.85, df = 6 (P = 0.18); I Test for overall effect: Z = 5.34 (P < 0.00001) Study or Subgroup Crispo A, et al. (2009)-Outside screening Dong W, et al. (2009)-Cutside screening Dong W, et al. (2009)-Cutside screening Dong W, et al. (2009)-Outside screening Falck AK, et al. (2016)-Symptomatic Falck AK, et al. (2016)-Symptomatic	Events 32 34 212 30 213 39 38 598 598 598 598 Detection (Screent Events 45 26 196 50 76	Total 108 405 1693 214 974 257 233 3884 ing) De Total 105 408 1021 204 243	Events 97 63 390 47 491 198 190 1476 Events 1476 465 70 301	methods) Total 324 541 2142 196 2013 1087 956 7259 hods) <u>Total W</u> 320 1 525 1 1255 1 185 1 1027 1	Weight           4.2%           6.1%           37.5%           5.2%           31.1%           8.0%           100.0%           eight         M           2.1%           8.0%           2.3%           5.5%	M-H, Fixed, 95% C           0.99 [0.61, 1.59]           0.70 [0.45, 1.08]           0.75 [0.45, 1.08]           0.64 [0.54, 0.77]           0.52 [0.31, 0.86]           0.87 [0.72, 1.04]           0.80 [0.55, 1.17]           0.75 [0.67, 0.83]           0.75 [0.67, 0.83]           0.75 [0.67, 0.83]           0.99 [0.38, 0.92]           0.37 [0.24, 0.59]           0.40 [0.33, 0.49]           0.33 [0.34, 0.82]           0.74 [0.40, 0.40]	2. M-H. Fixed. 95% Cl 	+ 10	
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D	Study or Subgroup Crispo A, et al. (2013)-Symptomatic Dawson SJ, et al. (2009)-Outside screening Dong W, et al. (2009)-Symptomatic Falck AK, et al. (2016)-Symptomatic Lehtimäki T, et al. (2016)-Symptomatic Lehtimäki T, et al. (2017)-Outside screening Silhto H, et al. (2018)-Outside screening Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 8.85, df = 6 (P = 0.18); I Test for overall effect: Z = 5.34 (P < 0.00001) Study or Subgroup Crispo A, et al. (2009)-Outside screening Dawson SJ, et al. (2009)-Symptomatic Dawson SJ, et al. (2009)-Symptomatic Falck AK, et al. (2016)-Symptomatic Falck AK, et al. (2016)-Symptomatic Joensu H, et al. (2004)-Outside screening Lehtimäki T, et al. (2011)-Outside screening Lehtimäki T, et al. (2008)-Outside screening	Events 32 34 212 30 213 39 38 598 <sup>2</sup> = 32% Detection (Screer Events 45 26 196 50 75 73 63	Total 108 405 1693 214 974 257 233 3884 105 408 1021 204 243 224 224 224 224	Events 97 63 390 47 491 198 190 1476 Events 179 86 465 70 391 379 325	hods) Total w 2013 1087 7259 hods) Total W 320 1087 956 7259 1085 1085 1085 1085 1085 1085 1085 1087	Weight           4.2%           6.1%           37.5%           5.2%           31.1%           8.0%           7.8%           100.0%           eight         M           2.1%           1.8%           8.0%           5.5%           5.4%           4.9%	M-H, Fixed, 95% C           0.99 (0.61, 1.59)           0.70 (0.45, 1.08)           0.75 (0.45, 1.08)           0.64 (0.54, 0.71)           0.52 (0.31, 0.86)           0.87 (0.72, 1.04)           0.80 (0.55, 1.17)           0.79 (0.54, 1.15)           0.75 (0.67, 0.83)           Odds Ratio           LH, Random, 95% CI           U.33, 0.49)           0.59 (0.38, 0.92)           0.73 (0.54, 0.88)           0.73 (0.54, 0.88)           0.76 (0.56, 1.04)           0.76 (0.56, 1.04)           0.76 (0.56, 1.04)           0.76 (0.56, 1.04)	Cl M-H. Fixed. 95% Cl 0.1 0.2 0.5 1 2 5 Detection (other methods) Favours [control] Odds Ratio M-H. Random. 95% Cl	+ 10	
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D	Study or Subgroup Crispo A, et al. (2013)-Symptomatic Dawson SJ, et al. (2009)-Outside screening Dong W, et al. (2008)-Symptomatic Falck AK, et al. (2016)-Symptomatic Lehtimäki T, et al. (2017)-Outside screening Sihto H, et al. (2012)-Outside screening Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 8.85, df = 6 (P = 0.18); I Test for overall effect: Z = 5.34 (P < 0.00001) Study or Subgroup Crispo A, et al. (2013)-Symptomatic Dawson SJ, et al. (2008)-Outside screening Dong W, et al. (2008)-Outside screening Dong W, et al. (2008)-Symptomatic Falck AK, et al. (2016)-Symptomatic Falck AK, et al. (2016)-Symptomatic Falck AK, et al. (2016)-Symptomatic Total (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = 0.07; Chi <sup>2</sup> = 22.64, df = 6 Heterogeneity: Tau <sup>2</sup> = 0.07; Chi <sup>2</sup> = 22.64, df = 6	Events           32           34           212           30           213           39           38 $^2 = 32\%$ 598           e = 32%           26           196           50           75           73           63           (P = 0.0009); I <sup>2</sup> =	Total           108           405           1693           214           974           257           233           3884           105           408           105           408           1021           243           228           214           243           214           243           214           2433           23%	Events 97 63 390 47 491 198 190 1476 Events 179 86 465 70 391 379 335	Total         W           324         544           544         2142           196         2013           1087         956           7259         1           559         1           1855         1           1855         1           1927         1           994         1           9902         1           5242         10	L Weight 4.2% 6.1% 37.5% 5.2% 37.5% 5.2% 100.0% 100.0% eight M 2.1% 1.8% 8.0% 2.3% 5.5% 5.4% 4.9% 100.0%	M-H, Fixed, 95% C           0.99 (0.61, 1.59)           0.70 (0.45, 1.08)           0.70 (0.45, 1.08)           0.64 (0.54, 0.71)           0.52 (0.31, 0.86)           0.87 (0.72, 1.04)           0.80 (0.55, 1.17)           0.79 (0.54, 1.15)           0.75 (0.67, 0.83)           UHL Random, 95% CI           0.59 [0.38, 0.92]           0.37 (0.24, 0.59)           0.73 (0.54, 0.98)           0.76 [0.56, 1.04]           0.71 [0.51, 0.98]           0.57 [0.45, 0.73]	M-H. Fixed. 95% Cl           0.1         0.2         0.5         1         2         5           Detection (other methods)         Favours [control]         Odds Ratio         MH. Random. 95% Cl           0.1         0.2         0.5         1         2         5           Detection (other methods)         Favours [control]         Odds Ratio         MH. Random. 95% Cl         4           0.1         0.2         0.5         1         2         5	10 +10	

**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.

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			8			
Analysis type	Patients	Ptudies	PHR (95% CI)	P value	l² (%)	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

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

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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