Prognostic and Clinicopathological Value of Cyclin E Expression in Breast Cancer: A Meta-Analysis

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Abstract

Background: Multiple studies have analyzed the correlation between Cyclin E and breast cancer prognosis, but the results are controversial. In this study, a meta-analysis was used to summarize the published reports, clarify the predictive value of Cyclin E in breast cancer, and the relationship with clinicopathological characteristics.

Methods: A systematic search was retrieved in PubMed, Embase, Web of Science, Cochrane Collaboration Library on the comprehensive search strategy up to 24 August 2020. recurrence-free survival (RFS), overall survival (OS), and breast cancer-specific survival (BCSS) was estimated using pooled hazard ratios (HRs) and risk ratios (RRs) with 95% confidence intervals (95% CIs) by univariate and multivariate analysis.

Results: Twenty-eight eligible studies met our inclusion criteria. The present meta-analysis indicates that high cyclin E expression is independently associated with poor OS, BCSS, and RFS in female breast cancer patients by univariate and multivariate analysis. Furthermore, higher histological grades, estrogen receptor (ER)-negativity, positive lymph node metastasis, younger patients, and premenopausal status were associated with Cyclin E overexpression.

Conclusions: High expression of Cyclin E is associated with poor breast cancer outcomes and relevant to multiple clinical characteristics.

Background

Breast cancer is the most common tumor among women and the leading cause of death. In 2018, there were about 2.1 million new cases of breast cancer and about 630,000 dead due to breast neoplasms [1]. The key to breast cancer treatment depends mainly on early diagnosis and accurate assessment of prognostic markers that predict the disease development to improve the patient's management.

At present, several independent prognostic factors have been determined, including tumor size, histological grade, lymph node status, hormone receptor status, HER-2 status, and patient age [2–4]. However, most potential prognostic biological markers have not been applied in clinical practice. It is worthy of recognition. Some molecular markers have the possibility of refining the risk assessment.

In the occurrence and progression of breast cancer, the disorder of cell cycle regulation is part of the leading causes of uncontrolled cell proliferation [5]. As a critical regulator of S phase entry, Cyclin E can be bind to and activate Cyclin-dependent kinase-2 (CDK-2) to directly promote G1 to S phase, showing prominent periodic expression in the cell cycle [6, 7]. The over-expression of Cyclin E can accelerate cell entry into the S phase, lead to unlimited cell proliferation, and further cause tumor occurrence and development [8]. Cyclin E is overexpressed in many human tumors, and its genome has been frequently amplified [9, 10]. Several studies have explored the relationship between Cyclin E and breast cancer patients. However, the prognostic value differs among the studies [11–14]. The reason may be due to the limited sample size, or there may be constant heterogeneity. To assess the influence of Cyclin E expression level on breast cancer and the relationship with clinicopathological characteristics, we performed this meta-analysis to evaluate the prognostic role of Cyclin E or a potential marker as a therapeutic target in breast cancer.

Methods

The meta-analysis was performed under the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidance [15]. PubMed, Embase, Cochrane Collaboration Library, and Web of science were searched before 24 August 2020.

Search strategy

The search strategy included the Mesh terms 'breast cancer' AND 'Cyclin E' AND 'prognosis/survival/prognostic/outcome' with all appropriate subheadings contained. An additional file shows this in more detail [see Additional file 1]. Besides, we manually retrieved references in the included study to identify the need for inclusion in the study.

Inclusion and exclusion criteria

Inclusion criteria: (1) full-text publication; (2) Studies on the correlation between Cyclin E and prognosis of breast cancer; (3) The subjects were female breast cancer patients diagnosed by pathology; (4) The HR or RR and its 95% CI or its corresponding survival curve were available for data extraction. Exclusion criteria were summarized as follows: (1) Systematic evaluation, meta-analysis, case reports, letters, and comments were excluded; (2) Non-human studies.; (3) The full text of the literature could not be obtained, or the data report was incomplete, or the HR or RR and its 95% CI could not be extracted; (4) Non-English literature.

Data extraction

The literature selection process is given in Fig. 1. Two independent researchers (Wang YF and Yang QJ) independently screened the literature and extracted the data depending on the inclusion and exclusion criteria. Any differentials in their assessment were resolved by discussion.

Various contents were extracted, including the first author, number of patients, publication year, age, AJCC stage, histological grade, Detection Method, cut-off value, follow-up period. The Kaplan Meier survival curves were read by Engauge Digitizer version 4.1 (<http://digitizer.sourceforge.net/>).

Statistical analysis

In this meta-analysis, HR or RR was used to measure the correlation between Cyclin E and the prognostic factors. Meanwhile, we also analyzed the relationship between Cyclin E and the clinicopathological characteristics. RR value and 95% CI were used for assessment. Heterogeneity among studying data was evaluated by χ^2 -based Q-tests and I^2 tests. The random-effect model was used only for high heterogeneity ($I^2 > 50\%$ or $P < 0.01$); otherwise, fixed-effect model was used [16]. Review Manager, version 5.3 (The Cochrane Collaboration, Copenhagen, Denmark) was used to conduct the meta-analysis. An HR or RR > 1 indicated a worse outcome for the positive group, and a P-value < 0.05 throughout was considered statistically significant. Publication bias was assessed by funnel plots [17, 18].

Results

Search results

A total of 1244 references were retrieved through systematic literature retrieval, of which 476 were duplicated, two were not available, and one was not in English. Through screening the titles and abstracts, 16 studies were non-clinical, 684 articles were unrelated to the study, 27 studies were guides, reviews, letters, or abstracts. After reading the full text, survival data could not be extracted from 9 articles. One article is updated. Finally, 28 studies were included [11–14, 19–42]. The selection flow chart is shown in Fig. 1.

Characteristics of eligible studies

The included literature was published between 1996 and 2020 and comprised 9289 patients (sample ranged from 56 to 2032 patients) with a median follow-up time ranging from 3 to 15 years. The studies were conducted in 13 countries, with ages ranging between 20 and 90 years (Table 1). Three methods were used to detect Cyclin E level: Western blotting (3 studies), IHC (20 studies), and RT-PCR (5 studies). The different cut-off values and different antibodies were documented by the studies. (Table 2). The prognostic indicators were: overall survival (OS), recurrence-free survival (RFS), and breast cancer-specific survival (BCSS). In our meta-analysis, the results of DFS and MFS were integrated into RFS, and the effect of Cyclin E on prognosis was analyzed from univariate and multivariate situations. (Additional file 2). Recurrence-free survival was defined as time to any type of recurrence or death from any cause. Overall survival was defined from the beginning of the random assignment to death from any cause. Breast cancer-specific survival was defined as time to death from breast cancer. The quality of the eligible literature was assessed using the Newcastle Ottawa Scale (NOS) criteria for cohort studies [43]. The scale evaluates articles from three aspects (selectivity, comparability, and exposure). A score of 7 or more is considered to be of high quality (Additional file 3).

Two studies were published on the relation between Cyclin E and breast cancer in 1996 and 1999, respectively [19, 44]. The latter one was an updated article, but they combined cyclin E with other factors when analyzing survival indicators, so we used the former, and only the 100 patients with stage I-III disease were included in the survival analysis. There were two studies [25, 26] based on the same patient cohort. Nevertheless, Kuhling et al.'s paper contained 59 patients who received anti-hormonal therapy, causing the survival data to be different, so both of them were included in the analysis. A similar situation occurred in another three articles [27, 30, 31], with varying amounts of sample leading to different data. Potemski et al. wrote two articles in 2009 and 2006 [36, 45], respectively. The paper of 2009 included larger samples from 1997 to 2001, so the 2006 paper was excluded. However, the relationship between Cyclin E and some clinicopathological features was included in this article, so it was used to analyze the relationship between Cyclin E and clinicopathological characteristics. Since the human genome encodes two E-type cyclins: Cyclin E 1(CCNE1) and Cyclin E 2(CCNE2), CCNE1 is the formerly cyclin E, which is located on chromosome 19q12-q13 (46, 47). Therefore, survival data from three articles [33, 34, 41] on CCNE1 were included in the study.

Table 1
Study crowd characteristics

First author, year	No. of Patients	Median age (years)	TNM Stage	Histological Grade	Median Follow-up (months)	Country	Specimen collection time	Adjuvant therapy	Outcomes	NOS
Nielsen et al. 1996 [19]	114	NR	II-II	NR	53 (23–80)	Sweden	1988–1991	CT, ET, RT	RFS, BCSS	8
Porter et al. 1997 [20]	278	20–40	NR	intermediate/high	62.4	USA	1983–1992	NR	OS, BCSS	7
Bukholm et al. 2001 [21]	170	60 (28–88)	NR	II-II	58.8 (5–144)	Norway	1988–1993	NR	BCSS, RFS	7
Donnellan et al. 2001 [22]	157	49	II-II	II-II	36	South Africa	1985–1997	CT, ET, RT	OS	8
Kim et al. 2001 [23]	128	NR	II-II	II-II	69.6(3.3–121.5)	Korea	1989–1992	CT, ET, RT	OS, RFS	8
Keyomarsi et al. 2002 [11]	395	64	II-II	NR	76.8	USA	1990–1995	NR	BCSS, OS	7
Han et al. 2003 [24]	175	NR	II-III	II-II	75(2–169)	Korea	1994–1997	CT, ET	OS	7
Kühling, H et al. 2003 [25]	332	61 (23–91)	II-III	NR	99 (24 – 208)	Sweden	1970–1986	NR	BCSS, RFS	8
Rudolph et al. 2003 [26]	273	61 (23–91)	II-III	NR	99 (24 – 208)	Sweden	1970–1986	NR	BCSS	7
Span et al. 2003 [13]	277	60 (31–88)	I-II	I-II	75(2-169)	Netherlands	1987–1997	CT, ET, RT	OS, RFS	7
Foulkes et al. 2004 [27]	241	65	NR	NR	95	Canada	1980–1995	NR	BCSS	7
Lindahl et al. 2004 [28]	270	63	NR	I-II	122	Sweden	1987–1999	CT, ET	OS	7
Peters et al. 2004 [29]	56	NR	II-III	I-II	NR	Argentina	1995–1999	CT, RT	RFS	7
Arnes et al. 2005 [30]	259	65	NR	I-II	117.6	Canada	1980–1995	NR	BCSS	8
Chappuis et al. 2005 [31]	278	65	NR	NR	96	Canada	1980–1995	CT, RT	BCSS	8
Brennan et al. 2006 [12]	400	50	III	NR	166.8	Sweden	1984–1991	CT, RT	BCSS	8
Callagy et al. 2006 [32]	651	48.5 (22–90)	I-II	NR	104.4 (4.8-472.8)	British	1970–1990	NR	OS	7
Desmedt et al. 2006 [33]	205	50	I-II	I-II	97.3	British	NR	NR	RFS	7
Porter et al. 2006 [14]	2032	47 (21–76)	I-II	NR	84	USA	1994–1997	CT	OS, RFS	7

First author, year	No. of Patients	Median age (years)	TNM Stage	Histological Grade	Median Follow-up (months)	Country	Specimen collection time	Adjuvant therapy	Outcomes	NOS
Sieuwertset al. 2006 [34]	635	56 (25–88)	I–II	NR	95 (11–202)	Netherlands	1979–1995	CT, ET, or RT	OS, RFS	8
Somlo et al. 2008 [35]	239	46 (26–62)	II–III	NR	86 (20–155)	USA	1989–2001	CT, ET, RT	OS, RFS	8
Potemski et al. 2009 [36]	174	50	I–II	NR	58 (1–78)	Poland	1997–2001	CT, RT, ET	BCSS	8
Sgambato et al. 2009 [37]	134	56 (32–77)	I–II	NR	72 (21–122)	Italy	1994–2001	CT, RT	OS	7
Lemée et al. 2010 [38]	206	18–64	I–II	NR	60	French	1997–2000	NR	OS	7
Tokai et al. 2011 [39]	69	55.6 (34–87)	I–II	NR	60	Japan	2000–2004	NR	OS, RFS	7
Voduc et al. 2008 [40]	438	60	I–II	NR	180	Canada	1974–1995	NR	BCSS	8
Lundgren et al. 2015 [41]	186	66	I–II	I–II	NR	Sweden	1993–2004	NR	BCSS	7
Johnston et al. 2020 [42]	517	≥ 70	I–II	NR	75.6 (73.2–80.4)	British	1973–2010	NR	OS, BCSS	8
Abbreviations: CT: chemotherapy; ET: endocrine therapy; RT: radiotherapy; NR: not reported; HR: hazard ratio; RR: risk ratio; RFS, recurrence-free survival; OS, overall survival. BCSS: breast cancer-specific survival.										

Table 2
Technical details of the method for Cyclin E quantification

First author, year	Detection method	Cut off	Antibody	Prevalence (high/total)
Nielsen et al. 1996 [19]	WB	≥ 0.5	NR	27% [▲] /29.8% [▮]
Porter et al. 1997 [20]	IHC	>benign breast epithelium	affinity-purified anti-Cyclin E	35%
Bukholm et al. 2001 [21]	IHC	> 30%	NR	21.8% (37/170)
Donnellan et al. 2001 [22]	IHC	> 5%	IgG2a kappa mouse monoclonal anti-Cyclin E antibody	46.2% (72/156)
Kim et al. 2001 [23]	IHC	> 50%	rabbit polyclonal anti-Cyclin E	40.6%(52/128)
Keyomarsi et al. 2002 [11]	WB	>benign breast epithelium	monoclonal antibody HE12	32%(125/395)
Han et al. 2003 [24]	IHC	> 10%	rabbit polyclonal IgG anti-Cyclin E	27.4% (48/175)
Kühling, H et al. 2003 [25]	IHC	> 10%	NR	NR
Rudolph et al. 2003 [26]	IHC	> 10%	NR	NR
Span et al. 2003 [13]	RT-PCR	NR	NR	28% (78/277)
Foulkes et al. 2004 [27]	IHC	>benign breast epithelium	affinity-purified anti-Cyclin E	26%(63/241)
Lindahl et al. 2004 [28]	IHC	$\geq 50\%$	mouse monoclonal anti-Cyclin E	10%(27/270)
Peters et al. 2004 [29]	IHC	> 10%	HE12, cat no. sc-247	58.9% (33/56)
Arnes et al. 2005 [30]	IHC	NR	affinity-purified anti-Cyclin E	NR
Chappuis et al. 2005 [31]	IHC	>benign breast epithelium	affinity-purified anti-Cyclin E	26.5%(67/253)
Brennan et al. 2006 [12]	IHC	> 25%	NR	NR
Callagy et al. 2006 [32]	IHC	> 25%	NR	NR
Desmedt et al. 2006 [33]	RT-PCR	NR	NR	NR
Porter et al. 2006 [14]	IHC	high scores:4–7	anti-Cyclin E polyclonal antibody	NR
Sieuwertset al. 2006 [34]	RT-PCR	0.03	NR	60.5%(384/635)
Somlo et al. 2008 [35]	RT-PCR	> 0.9	NR	25.2% (31/123)
Potemski et al. 2009 [36]	IHC	$\geq 2\%$	anti-Cyclin E monoclonal antibody	56.9% (99/174)
Sgambato et al. 2009 [37]	IHC	> 11%	NR	34.3% (46/134)
Lemée et al. 2010 [38]	RT-PCR	> 0.182	NR	NR
Tokai et al. 2011 [39]	WB	NR	NR	65.2% (45/69)
Voduc et al. 2008 [40]	IHC	> 10%	mouse monoclonal anti-Cyclin E	46% (146/319)
Lundgren et al. 2015 [41]	IHC	> 20%	anti-Cyclin E monoclonal antibody	NA
Johnston et al. 2020 [42]	IHC	> 5%	mouse monoclonal antibodies and rabbit polyclonal antibodies	38.6% (199/516)
Abbreviations: [▲] Prevalence of Cyclin E in patients of stage I–III. [▮] Prevalence of Cyclin E in patients of stage I–IV; WB: Western blot; IHC, immunohistochemistry; RT-PCR: reverse transcription-polymerase chain reaction; NR: not reported.				

Table 3
Correlation between high Cyclin E level and clinicopathological parameters

Outcome	boundary	Studies	Patients	Heterogeneity	Model	RR [95%CI]	P-value
Age	≤50 years; ≥50 years	4		P = 0.03; I ² = 66%	REM	1.56 [1.03, 2.34]	0.03
Tumor size	≤20mm; ≥20 mm	9		P = 0.02; I ² = 56%	REM	0.86 [0.70, 1.05]	0.14
ER status	+/-	10		P < 0.0001; I ² = 90%	REM	0.56 [0.38, 0.84]	0.005
PR status	+/-	4		P < 0.0001; I ² = 91%	REM	0.80 [0.45, 1.44]	0.46
Disease stage	I/II	5		P = 0.98; I ² = 0%	FEM	0.83 [0.67, 1.01]	0.07
Histological type	Ductal/Lobular	2		P = 0.20; I ² = 39%	FEM	1.39 [0.75, 2.56]	0.30
Histological grade	I/II	6		P < 0.0001; I ² = 87%	REM	0.41 [0.17, 0.99]	0.05
lymph node status	+/-	8		P = 0.08; I ² = 44%	FEM	1.29 [1.11, 1.50]	0.0009
Menopausal status	Pre/Post	3		P = 0.16; I ² = 46%	FEM	1.58 [1.11, 2.23]	0.01
HER2 status	+/-	3		P = 0.68; I ² = 0%	FEM	1.11 [0.92, 1.33]	0.27
Nuclear stage	I/II	2		P = 0.12; I ² = 59%	REM	1.03 [0.51, 2.07]	0.93
Abbreviations: RR: risk ratio; FEM: fixed effect model; REM: random effect model; HER2: Human epidermal growth factor receptor-2.							

Outcomes

Impact of cyclin E level on BCSS

A total of 13 articles assessed the relationship between Cyclin E and BCSS in breast cancer patients. The result suggested that high Cyclin E expression was a prognostic indicator of poor BCSS both in univariate and multivariate analysis using RR (2.06, 95%CI, 1.48–2.87, P < 0.0001; 2.52, 95%CI, 1.70–3.74, p < 0.00001) as shown in Fig. 2C and 2D. When HR was used, high Cyclin E overexpression was only statistically significantly associated with poor BCSS in univariate analysis. The combined HR for BCSS was 2.62, with a 95% CI 1.26–5.42 (p = 0.01), as shown in Fig. 2A. The multivariate analysis results were close to statistical significance (HR, 2.08, 95%CI, 0.91–4.78, P = 0.08), as shown in Fig. 2B. Heterogeneity was high for the results. Thus, a random-effects model was used.

Impact of cyclin E level on OS

Fifteen articles analyzed the relationship between Cyclin E and OS. High Cyclin E expression served as a marker of reduced overall survival in all patients. In univariate analysis, worse OS (HR 1.85, 95% CI 1.31–2.59; P < 0.0004; RR 1.93, 95% CI 1.32–2.81; P = 0.0006) were observed among patients considered as Cyclin E positive (Fig. 3A and 3C) therefore the random-effect model was used for significant heterogeneity (P = 0.003, I² = 67%; P = 0.03, I² = 63%). For the multivariate analysis, worse OS was found in the breast cancer patients with Cyclin E overexpression (HR 2.36, 95% CI 1.78–3.12; P < 0.00001; RR 3.10, 95% CI 2.08–4.63; P < 0.00001) as shown in Fig. 3B and 3D. Since there was no heterogeneity (P = 0.88, I² = 0%; P = 0.48, I² = 0%), a fixed-effect model was applied.

Impact of cyclin E level on RFS

The pooled HR for recurrence-free survival (RFS) was reported in seven studies. We found that worse RFS (HR 1.88, 95% CI 1.15–3.07; p = 0.01) was observed among patients considered Cyclin E positive in univariate analysis (Fig. 4A), since the random-effects model was used for significant heterogeneity (P < 0.00001, I² = 87%). While, high cyclin E expression levels showed significant association with poor RFS (RR 1.98, 95% CI 1.28–3.08; p = 0.002) in the multivariate analysis while not significant in a univariate model (RR 2.56, 95%CI 0.89–7.43, p = 0.08) (Fig. 4B, 4C).

Relationship between Cyclin E and clinicopathological features

We also investigated the relationship between Cyclin E and clinicopathological characteristics. The pooled results showed that Cyclin E expression was increased in patients with young age (RR = 1.56, 95% CI, 1.03–2.34; P = 0.03), estrogen receptor (ER)-negativity (RR = 1.77, 95% CI, 1.19–2.64; P = 0.005), premenopausal status (RR = 1.58, 95% CI 1.11–2.23; P = 0.01) and lymph node-positivity (RR = 1.29, 95% CI, 1.11–1.50; P = 0.0009). High histological grade was a borderline significance (RR = 2.46, 95% CI, 1.01–5.96; P = 0.05). However, other clinicopathological

factors were not correlated with Cyclin E overexpression, including tumor size, PR status, disease stage, histological type, HER2 status, and nuclear stage (Table 3), the forest plots were shown in Additional file 4.

Any deletion of the literature in this study will not affect the results of this study, which means that the calculation results of the above random effect are stable and reliable. In the subgroup studies with more than five included literature, funnel plots were used to evaluate publication bias (Fig. 5). As can be seen from the figures, funnel plots of each study were basically symmetrical, so it can be judged that there was no publication bias in this study.

Discussion

Breast cancer is a complex process involving multiple factors, one of the most critical aspects is the disorder of cell cycle regulation [5]. Accurate prediction of prognosis is one of the most critical problems in breast cancer treatment. The prediction of breast cancer is closely related to the disease stage, and early diagnosis of the disease is crucial to the patient's prognosis. Once the risk of recurrence has been determined, it can be used to evaluate the potential effects of endocrine therapy, chemotherapy, or a combination of these treatments. The determination of accurate prognostic indicators will also influence the patient's individualized treatment. Also, identifying prognostic factors with potential biological significance can be used as therapeutic targets, which will be of great relevance to identifying and treating high-risk patients. The cell cycle is divided into several stages artificially, including G0/G1, S, G2, and M phase. Cyclins play different roles at different cell cycle stages depending on their sequence primitives, expression, and activation forms [48]. Cyclins, along with the cyclin-dependent kinase (CDKs) and cyclin-dependent kinase inhibitors (CKIs), constitute the cycle regulation system to ensure the cell cycle orderly [49]. The limitation point of transition from the G1 to the S1 phase is crucial for cell proliferation and differentiation [50]. The primary function of Cyclin E is to regulate the restriction point "R" at the end of the G1-phase to allow cells to enter the S phase [51, 52]. The restriction point "R" was found to be the endpoint in the transition of the G1 to S phase of the cell cycle, which plays a crucial role in cell regulation and prevents the excessive and unrestricted proliferation of cells. It was found that overexpression of Cyclin E could accelerate the G1 phase of the cell cycle [53]. The destruction of these pathways or the absence or overexpression of specific factors is closely related to the malignant transformation of cells and cancer development [54]. Cyclin E expression levels are elevated significantly in many human tumors, manifested by amplification of the genome locus at which it is located (19q12-Q13) [55, 56], leading to widespread concern about its role in tumors. The over-expressed Cyclin E manifests as different molecular phenotypes in breast cancer and issue in the inactivation of the pRb pathway. A lower molecule form of Cyclin E derived from calpain induces a higher kinase activity [57, 58]. It has been pointed out that the oncogenic activity of Cyclin E can be inhibited by truncating the protein [59]. At present, many studies have assessed that the overexpression of Cyclin E may be a prognostic factor of breast cancer patients. Most of the research shows that Cyclin E can indicate breast cancer prognosis, but other studies could not confirm this finding. The present meta-analysis is an updated one to investigate the correlation between Cyclin E expression and breast cancer prognosis.

In this study, a quantitative and systematic analysis was conducted on the published literature. Through reasonable inclusion and exclusion criteria, available literature was obtained, and relevant data were extracted. The correlation between the high expression of Cyclin E in breast cancer and prognosis and clinicopathological characteristics were analyzed systematically.

As the data are shown above, our meta-analysis results demonstrate that Cyclin E overexpression was statistically significantly associated with worse OS, BCSS, and RFS either in univariate or multivariate analysis in the overall population. In contrast to the previous two meta-analyses [60, 61]. Our results suggest that Cyclin E overexpression is associated with poor RFS, which is different from previous studies.

In the original studies, the authors used hazard ratios and risk ratios to analyze the association between Cyclin E and prognosis in breast cancer patients using univariate and multivariate analyses. RR is a measure of the strength of the association between exposure and outcome, that is, the ratio of morbidity or mortality in the exposed group to that in the non-exposed group, and applies to cohort studies or randomized controlled trials. RR indicates how many times the risk of morbidity or death in the exposed group is that of the non-exposed group. The more significant the RR value, the greater the effect of exposure, the stronger the association between exposure and outcome. The hazard ratio (HR), which is the ratio of the risk function of the exposed group to the non-exposed group, is generally obtained from the Cox proportional risk model. Most people think that HR and RR mean the same thing, but HR has a time factor. In other words, RR with time effect is HR. In the survival data, RR takes into account the difference in endpoint events, while HR takes into account the presence of endpoint events and the time taken to reach the endpoint. Therefore, there are differences between the two, and it is necessary to analyze them separately. Besides, in some literature, Cyclin E was a statistically significant prognostic indicator in univariate analysis, but not in multivariate analysis, so we also analyzed it from two aspects. Meanwhile, we also analyzed the relationship between Cyclin E and different clinical characteristics. Cyclin E overexpression was significantly correlated with age, ER status, menopausal status, and lymph node metastasis, but not with tumor size, PR status, disease stage, histological type, HER2 status, and nuclear grade.

Several limitations are present in this meta-analysis. First, cyclin E positivity was evaluated using different methods, antibodies, scoring methods, and high Cyclin E is defined according to the cut-off chosen by each author. Therefore, heterogeneities exist in cut-offs of a high level of cyclin E. Keyomarsi K et al. [62] reported that tumor cells often overexpress low-molecular-weight (LMW) cyclin E forms, which was obtained

by cleaving Cyclin E with elastase [63]. LMW has a high prognostic value in primary breast cancer [13, 22, 24]. However, some immunohistochemical assays lack antibodies to detect the amino terminus that may lead to the differences in the prognostic value of Cyclin E in previous studies. Second, the differences in selected patients, adjuvant therapy resulted in bias in the analysis. Moreover, all samples in the studies were obtained through modified radical mastectomy or breast-conserving surgery, and most of the studies clearly stated that no preoperative anti-tumor therapy had been given. Meanwhile, some articles did not mention preoperative treatment, which may affect the detection of Cyclin E. Therefore, the combined results should be interpreted with caution.

Conclusion

In conclusion, our results suggest that high expression of Cyclin E may be a prognostic marker for poor OS, BCSS, and RFS regardless of age, HR status, and axillary lymph node status. Cyclin E overexpression was significantly associated with a range of clinicopathological parameters, such as age, lymph node metastasis, ER-negative and menopausal status. This information may help clinicians screen patients for anti-cyclin E therapy. To determine the role of Cyclin E expression in breast cancer, high-quality studies in more extensive, homogeneous populations are needed.

Abbreviations

CT

chemotherapy; ET: endocrine therapy; RT: radiotherapy; HR: hazard ratio; RR: risk ratio; CI: Confidence interval; RFS, recurrence-free survival; OS, overall survival. BCSS: breast cancer-specific survival; WB: Western blot; IHC, immunohistochemistry; RT-PCR: reverse transcription-polymerase chain reaction; HER2: Human epidermal growth factor receptor-2; NR: not reported.

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not Applicable.

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of interest

The authors declare that they have no competing interests.

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Authors' contributions

WYF and MZJ designed the study. WYF and YQJ searched the literature and collected data, analyzed and drafted the manuscript. MZJ, WXW, and MDS reviewed and revised the manuscript. All authors read and approved the final manuscript.

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Not applicable.

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Supplementary Information

Additional file 1. Searching strategy

Additional file 2. Survival data indicator of original articles

Additional file 3. Quality assessment of the eligible studies

Additional file 4. Forest plots of the relationship between Cyclin E and clinicopathological features

Figures

Figure 1

Literature screening flow chart

Figure 2

Estimated HRs and RRs summary for BCSS

Figure 3

Estimated HRs and RRs summary for OS

Figure 4

Estimated HRs and RRs summary for RFS

Figure 5

Funnel plots of studies

Supplementary Files

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