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PRECLINICAL STUDY

The impact of cyclin D1 overexpression on the prognosis of ER-positive breast cancers: a meta-analysis

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Abstract Cyclin D1 (CCND1), a key regulator of cell cycle progression, is overexpressed in many human cancers, including breast cancer. However, the impact of CCND1 overexpression in these cancers remains unclear and controversial. We conducted a systematic literature search in PubMed and EMBASE with the search terms "cyclin D1", "CCND1", "breast cancer", "prognosis", and potential studies for analysis were selected. Studies with survival data, including progression-free survival (PFS), overall survival (OS) or metastasis-free survival (MFS), were included in this meta-analysis. A total of 33 studies containing 8,537 cases were included. The combined hazard risk (HR) and its 95 % confidence interval (CI) of OS, PFS and MFS were 1.13 (95 % CI 0.87–1.47; $P = 0.35$), 1.25 (95 % CI 0.95–1.64; $P = 0.12$), and 1.04 (95 % CI 0.80–1.36; $P = 0.76$), respectively, for primary breast cancer patients with tumors exhibiting CCND1 overexpression. Interestingly, the impact of CCND1 expression on OS was a 1.67-fold (95 % CI 1.38–2.02; $P = 0.00$) increased risk for ER-positive breast cancer patients. However, CCND1 overexpression exhibited no association with the PFS or OS of patients who received epirubicin-based neoadjuvant chemotherapy, for which the P values were 0.63 and 0.47, respectively. In summary, CCND1 overexpression impacts the prognosis of ER-positive breast cancer patients, but not patients with unselected primary breast cancer or patients treated with neoadjuvant chemotherapy.

Keywords Cyclin D1 · CCND1 · Breast cancer · Estrogen receptor · Prognosis

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Introduction

Breast cancer was the most frequent cancer among women in 2008 (23 % of all cancers), and ranks second overall (10.9 % of all cancers). Despite the development of combined therapeutic modalities and the prolonged overall survival (OS) and progression-free survival (PFS) of breast cancer patients, breast cancer remains the fifth leading cause of overall cancer deaths and the most frequent cause of cancer deaths in women [1]. Thus, identifying specific biomarkers that could serve as prognostic factors for breast cancer patients is crucial for individualized treatments. To date, several biomarkers have been demonstrated to impact the survival of breast cancer patients, including P27 [2], VEGF [3], COX-2 [4], and BCL-2 [5].

Cyclin D1 (CCND1) is located on chromosome 11q13 [6], is a key regulator of cell cycle progression, and functions as an oncogene in many human cancers, including breast cancer. As a G1 cyclin, it is a major positive regulator of the G1 restriction point [7]. Moreover, it contributes to the action of estrogen receptor (ER) in breast cancer

patients. As a cellular sensor for the presence of ER, it has been demonstrated to contribute significantly to ER activation in breast cancers [8].

CCND1 overexpression in breast cancer has been reported in various studies [9–30]. However, whether CCND1 represents a prognostic biomarker remains controversial. In this study, we conducted a systematic review and meta-analysis to estimate the effect of CCND1 overexpression on the survival of breast cancer patients.

Materials and methods

Literature research and selection

We identified studies via a literature search using the PubMed and EMBASE databases with "cyclin D1," "CCND1," "breast cancer," and "prognosis" as the search terms for publications published from January 1, 1966, through March 1, 2012. The titles and abstracts of the studies were first scanned to exclude all irrelevant papers. Then, we established the inclusion of the final studies by reading the full text of the remaining articles. Additional articles were identified through the references cited within the first series of selected articles. If more than one study reported the same cases, only the study with the most complete data was included.

The inclusion criteria for the articles examined in this study were as follows: (1) the study should be published in English; (2) total cases should be more than 40; (3) the study should be limited to research on human primary breast cancer; (4) the patients should be female; (5) the study should provide survival information, such as PFS, OS, and metastasis-free survival (MFS); and (6) the minimal follow-up time should be greater than 5 years.

Data extraction and quality assessment

Information was carefully extracted from all of the eligible studies by two independent investigators, according to the inclusion criteria detailed above. OS, MFS, and PFS were selected as the clinical outcomes for prognosis. The following information was collected: the name of the first author, year of publication, source of patients, study design, sample size, histology, stage, CCND1 overexpression (%), the hazard risk (HR) and its 95 % confidence interval (CI) of OS, HR (95 % CI) of PFS, and HR (95 % CI) of MFS.

The studies were assessed for quality using REMARK (Reporting recommendations for tumor MARKer prognostic studies) [31], and the definitions of the 18 items for reporting study quality provided by Chen et. al [32].

Statistical methods

The methods reported by Parmar et al. [33] for calculating the HR and its 95 % CI for survival data were consistent with those of our previous study [34]. HR describes the relative risk of complications based on a comparison of event rates. Moreover, it allows for including both censoring and time to event to represent the overall reduction in the risk of death compared to the control during the follow-up period. The HR calculations spreadsheet provided by Tierney et al. [35] was used to obtain the HR and its 95 % CI. Some of the following data were collected to summarize the HR from published summary statistics or the data extracted from Kaplan–Meier curves: observed events, expected events, total events, HR rate, variance, the patients in each arm, follow-up details, Kaplan–Meier curves and P value of log rank. Mantel–Haenszel or Cox analyses using Enguage Digitizer 4.1 were used to extract the data from Kaplan–Meier curves. In certain studies, the prognostic value of different variables for clinical outcomes was estimated using both multivariate and univariate analyses. In this case, the results of the multivariate analyses were used to calculate the HR.

Based on Peto's method [36], χ^2 tests were used to assess heterogeneity. I^2 statistics were performed to assess heterogeneity, where $I^2 < 50$ % was considered acceptable. If significant heterogeneity was observed, subgroup analysis was conducted to determine the cause of the heterogeneity. If significant heterogeneity persisted, a random-effects model was used for meta-analysis. Otherwise, the fixed-effects model was applied. Sensitivity analysis was performed to confirm the validity of our meta-analysis. Finally, both Begg's funnel plots and Egger's tests were performed to assess the publication bias of the literature. All of the tests were two sided, and P values <0.05 were regarded as statistically significant. The results were analyzed and confirmed by two individuals.

Results

Literature search

A total of 307 articles were identified. After screening the titles and abstracts, 226 articles were excluded because they were laboratory studies, review articles, case reports, male breast cancer, published in other languages, other tumors, total cases less than 40, or were irrelevant to this study. Eighty articles remained for full text review. Finally, 33 articles were included in this study after the exclusion of studies that lacked prognostic data or that reported repeated cases [37–40] (Fig. 1).

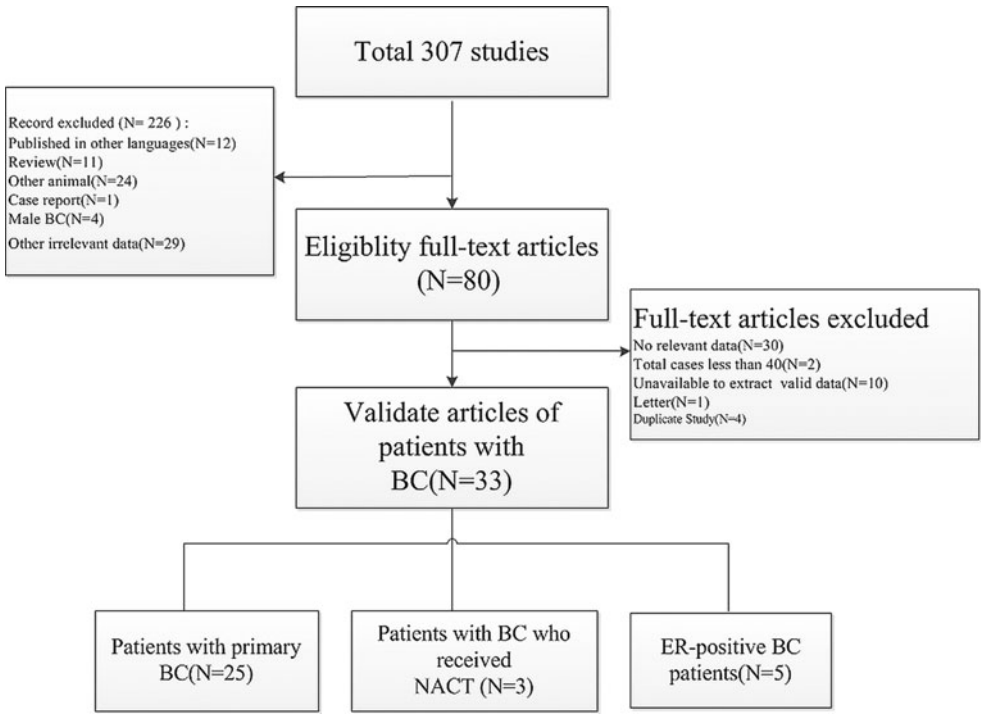

Fig. 1 Brief flow chart. *N* number, *BC* breast cancer, *NACT* neoadjuvant therapy

Study characteristics

The characteristics of the 33 selected studies [9–30, 39, 41–50] containing 8,537 cases are shown in Table 1. The studies were published from 1995 to 2013. Among them, 30 studies discussed the impacts of CCND1 overexpression on primary breast cancer patients who did not have any other pre-operative treatment, including radiotherapy, target therapy, endocrine therapy, and chemotherapy. Three studies investigated primary breast cancer patients who received epirubicin-based neoadjuvant chemotherapy. Five studies investigated ER-positive breast cancer patients. In these studies, most patients were hospitalized and diagnosed in the affiliated hospital of a medical college. Choschzick et al. [11] and Rudas et al. [25] only studied ER-positive breast cancer patients, whereas Umekita et al. [28], Elsheikh et al. [42], and Kenny et al. [15] included the survival data of all patients, including ER-positive patients. Several methods were used to assess CCND1 expression, including immunohistochemistry (IHC), polymerase chain reaction (PCR), tissue microarrays (TMAs), and northern blots (NBs). However, IHC was the most commonly used method. CCND1 gene amplification [39, 41–43], CCND1 mRNA overexpression [12, 13, 15, 24, 28, 29], and/or CCND1 protein overexpression were detected in these studies. Most of the studies detected CCND1 overexpression in tissue samples, with the exception of one study, which detected CCND1 in plasma [12]. The IHC evaluation of CCND1 produced variable positivity ranging from 12.9 to 70.1 % for breast cancers, possibly because of the diversity of antibodies and evaluation criteria used. In addition, Rudas et al. [25] reported the results of two randomized controlled trials, which we treated as two studies in the meta-analysis. The median follow-up time ranged from 48 to 132 months, whereas the minimum follow-up time ranged from 2 to 24 months, and the maximum follow-up time ranged from 97 to 176 months.

Main analysis

CCND1 overexpression and prognosis

Twenty-two studies investigated OS in a total of 4,009 unselected cases. Due to significant heterogeneity among the studies ($P = 0.22$; $I^{2-} = 63.5$ %), a random-effects model was used. However, no statistically significant risk (HR 1.13, 95 % CI 0.87–1.47; $P = 0.35$) was observed for CCND1 overexpression in breast cancer (Fig 2a). Furthermore, subgroup analysis was performed according to the methods used to detect CCND1 overexpression, analysis methods for survival data, histology, region, and study design. However, none of the results exhibited significant differences.

Eleven studies including 3,685 cases were evaluated for the effect of CCND1 overexpression on PFS (Fig 2b). A random-effects model was used to combine HRs because of the heterogeneity observed among the studies ($\chi^2 = 31.78$, $P = 0.00$, $I^2 = 68.5$ %). The pooled HR was 1.25 (95 % CI 0.95–1.64; $P = 0.12$).

Table 1 Study characteristics

First author	Years	Patient source	Method	Design	Patient characteristics	Histology	Stage	CCND1 overexpression (%)	HR (95 % CI) of OS	HR (95 % CI) of PFS	HR (95 % CI) of MFS
Pelosio [23]	1996	Italy	IHC	Retrospective	Unselected	Invasive breast cancer	II–III	117/167 (70.1 %)	MVA: 0.67 (0.39–1.14)	0.51 (0.32–0.81)	NR
Michalides [21]	1996	Netherlands	IHC	Cohort	Unselected	Unselected	I–II	85/248 (34.3 %)	MVA: 1.03 (0.7–1.52)	1.27 (0.83–1.93)	NR
Guo [13]	2007	China	IHC	Retrospective	Unselected	Unselected	I–III	55/98 (56.1 %)	MVA: 2.05 (1.08–3.89)	NR	NR
Bukholm [10]	2001	Norway	IHC	Cohort	Unselected	Unselected	NR	22/170 (12.9 %)	MVA: 0.76 (0.33–1.78)	NR	NR
Lee [16]	2007	Korea	IHC	Retrospective	Unselected	Invasive ductal cancer	I–III	209/327 (63.9 %)	MVA: 0.83 (0.54–1.29)	NR	NR
Lim [17]	2003	Korea	IHC	Retrospective	Unselected	Invasive ductal cancer	I–III	85/128 (66.4 %)	MVA: 0.31 (0.14–0.69)	NR	NR
Mclntosh [20]	1995	UK	IHC	Retrospective	Unselected	Unselected	NR	26/91 (28.6 %)	MVA: 1.1 (0.3–4.05)	1.35 (0.64–2.83)	NR
Millar [22]	2009	USA	IHC	Cohort	Unselected	Unselected	NR	52/175 (29.7 %)	MVA: 2.38 (1.254.52); UVA: 2.61 (1.20–3.92)	NR	NR
van Diest [30]	1997	USA	IHC	Retrospective	Unselected	Invasive breast cancer	I–II	87/148 (58.7 %)	UVA: 0.76 (0.43–1.34)	NR	NR
Lin [18]	2000	USA	IHC	Retrospective	Unselected	Unselected	NR	53/123 (56.9 %)	UVA: 1.72 (1.01–2.94)	NR	NR
Takano [26]	1999	Japan	IHC	Retrospective	Unselected	Invasive ductal cancer	NR	37/117 (31.6 %)	UVA: 2.2 (0.64–7.59)	NR	NR
Umekita (ER+)	2002	Japan	IHC	Retrospective	ER(+)	Invasive ductal cancer	NR	16/75 (21.3 %)	MVA: 3.45 (1.22–9.81); UVA: 3.53 (1.24–10.02)	4.54 (1.6–12.9)	NR
Umekita (ER−)	2002	Japan	IHC	Retrospective	ER(−)	Invasive ductal cancer	NR	57/98 (58.2 %)	MVA: 1.33 (0.48–3.71); UVA: 1.03 (0.37–2.88)	2.02 (0.79–5.16)	NR
Umekita [28]	2003	Japan	IHC	Retrospective	Unselected	Invasive ductal cancer	NR	73/173 (42.2 %)	MVA: 2.12 (1.02–4.40); UVA: 1.89 (0.91–3.92)	2.90 (1.44–5.83)	NR
Kenny [15]	1999	UK	NB	Retrospective	Unselected	Unselected	I–II	127/253 (50.2 %)	UVA: 1.22 (0.70–2.11)	1.37 (0.92–2.05)	NR
			NB	Retrospective	ER(+)	Unselected	I–II	108/182 (59.3 %)	UVA: 2.02 (1.09–3.74)	1.94 (1.13–3.36)	NR
Utsumi [29]	2000	Japan	PCR	Retrospective	Unselected	Invasive breast cancer	NR	48/97 (49.5 %)	MVA: 0.43 (0.16–1.19); UVA: 0.32 (0.12–0.89)	4.919 (1.41–17.14)	NR
Garcia [12]	2008	Spain	PCR	Prospective	Unselected	Unselected	I–III	105/125 (84.0 %)	UVA: 2.89 (0.92–9.04)	NR	NR
Peurala [24]	2013	Finland	IHC	Retrospective	Unselected	Unselected	I–IV	102/163 (62.6 %)	UVA:3.93 (1.23–12.6)	NR	NR
Ahnstrom [9]	2005	Sweden	IHC	Cohort	Unselected	Unselected	II–IV	54/230 (23.5 %)	NR	0.84 (0.54–1.3)	NR
Lundgren [19]	2012	UK	IHC	Cohort	Unselected	Unselected	NR	278/1038 (26.8 %)	NR	0.85 (0.91–0.64)	NR
Tobin [27]	2012	UK	IHC	Cohort	Unselected	Invasive ductal cancer	NR	170/470 (36.2 %)	NR	1.75 (1.05–2.89)	NR
Rudas [25]	2008	Austria	IHC	Retrospective	ER(+)	Unselected	I–II	140/253 (55.3 %)	MVA: 2.47 (1.08–5.03); UVA: 2.97 (1.34–6.55)	2.73 (1.5–4.96)	NR
			IHC	Retrospective	ER(+)	Unselected	I–II	569/948 (60.0 %)	MVA: 1.78 (1.36–2.34); UVA: 1.93 (1.47–2.52)	1.52 (1.14–2.04)	NR
Choschzick [11]	2010	Germany	TMA	Retrospective	ER(+)	Unselected	I–II	126/553 (22.8 %)	UVA: 1.38 (0.87–2.2)	NR	NR
Aaltonen [44]	2009	Finland	IHC	Retrospective	Unselected	Invasive breast cancer	NR	Total: 466 cases	NR	NR	0.93 (3.24–0.08)
Jacquemier [45]	2009	France	IHC	Retrospective	Unselected	Invasive adenocancers	I–III	284/690 (41.2 %)	NR	NR	0.65 (1.27–0.56)
Kreike [46]	2010	Netherlands	TMA	Retrospective	Unselected	Unselected	NR	25/295 (8.5 %)	NR	NR	0.36 (3.57–0.82)

Table 1 continued

First author	Years	Patient source	Method	Design	Patient characteristics	Histology	Stage	CCND1 overexpression (%)	HR (95 % CI) of OS	HR (95 % CI) of PFS	HR (95 % CI) of MFS
Perez-Tenorio [47]	2011	Sweden	PCR	Cohort	Unselected	Unselected	NR	24/190 (12.6 %)	NR	NR	0.46 (1.99–0.90)
Wachter [50]	2012	Germany	IHC	Retrospective	EC	Invasive breast cancer	NR	Total: 100 cases	MVA: 1.06 (0.89–1.28)	1.02 (0.86–1.21)	NR
Bonnefoi [48]	2003	Switzerland	IHC	Prospective	FEC or EC	Locally advanced and/or inflammatory breast cancers	III	52/178 (29.2 %)	MVA:0.91 (0.58–1.43); UVA:0.65 (0.40–1.04)	0.7 (0.46–1.07)	NR
Chen [49]	2012	China	IHC	Prospective	NE or CEF	Invasive ductal cancer	II–III	75/199 (37.7 %)	MVA:2.50 (1.20–6.40)	2.50 (1.30–4.60)	NR
Hwang [14]	2003	Korea	IHC	Retrospective study	Unselected	Invasive ductal cancer	I–III	118/175 (67.4 %)	MVA:0.79 (0.32–1.94)	NR	NR
Elsheikh [42]	2009	UK	TMA	Cohort	Unselected	Unselected	I–IV	49/475 (10.3 %)	MVA: 2.57 (1.04–6.35); UVA: 1.50 (0.72–3.14)	0.97 (0.41–2.28)	NR
Elsheikh (ER +)	2009	UK	TMA	Cohort	ER(+)	Unselected	I–IV	49/475 (10.4 %)	UVA: 2.00 (1.17–3.41)	NR	NR
Bostner [41]	2007	Sweden	PCR	Cohort	Unselected	Unselected	II–IV	28/244 (12.5 %)	NR	1.59 (0.96–2.64)	NR
Husdal [39]	2006	Norway	PCR	Cohort	Unselected	Invasive breast cancer	NR	64/82 (74.4 %)	MVA: 0.34 (0.10–1.00)	NR	NR
Rodriguez [43]	2004	France	SB	Retrospective study	Unselected	Unselected	NR	38/296 (12.8 %)	MVA: 1.60 (0.70–3.60)	2.20 (1.20–4.20)	NR

IHC immunohistochemistry, *MVA* multivariate analysis, *NR* not reported, *UVA* univariate analysis, *ER*(+) ER-positive, *NB* northern blotting, *PCR* polymerase chain reaction, *TMA* tissue microarrays, *EC* epirubicin + cyclophosphamide, *FEC* fluorouracil + epirubicin + cyclophosphamide, *NE* navelbine + epirubicin, *CEF* cyclophosphamide + epirubicin + 5′-fluorouracil, *SB* southern blotting

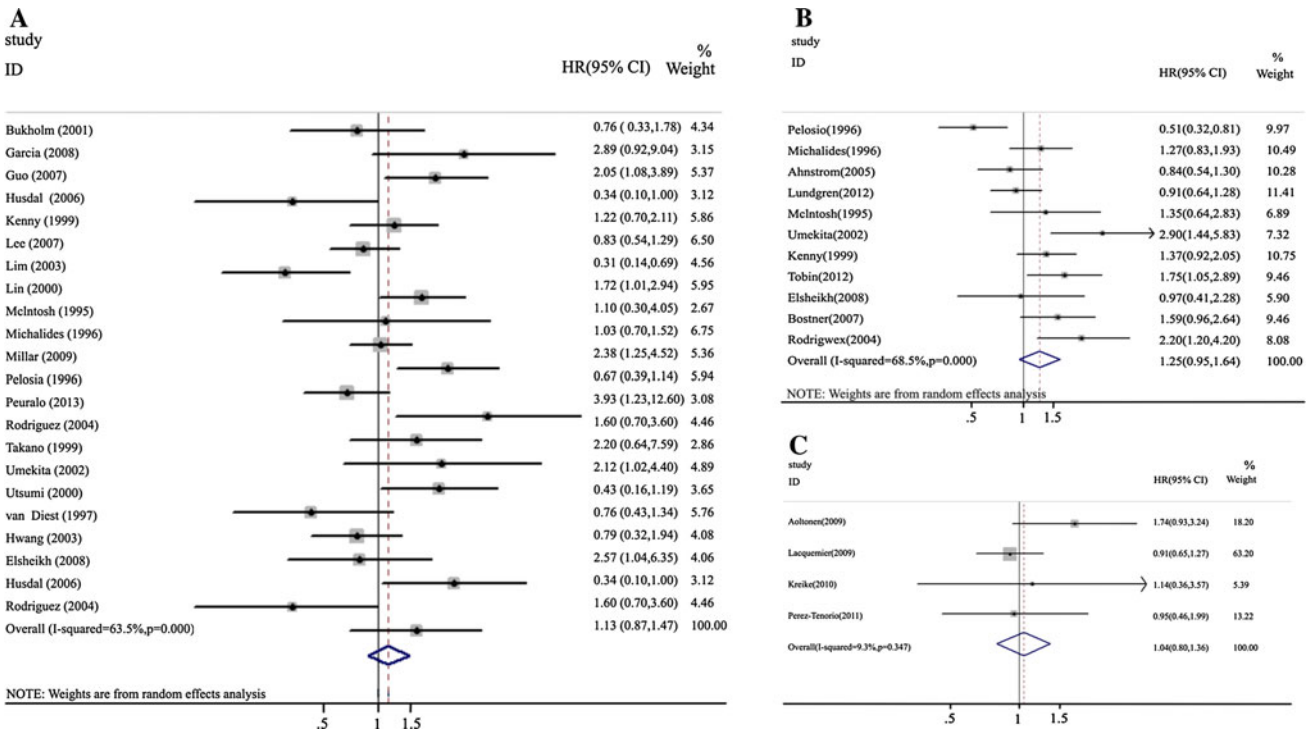

Fig. 2 A forest plot of the OS (**a**), PFS (**b**), and MFS (**c**) in unselected primary breast cancers

The results from four studies ($n = 1{,}941$) on the relationship between CCND1 expression and MFS were also negative (Fig 2c). Because low homogeneity ($\chi^2 = 147.75$, $P = 0.00$, $I^2 = 87.1$ %) was detected, a random-effects model was used to calculate the HR (1.04, 95 % CI 0.80–1.36; $P = 0.76$).

CCND1 overexpression and ER-positive patients

A total of five studies including 2,580 cases were evaluated for the impact of CCND1 expression on the OS of ER-positive breast cancer patients. A fixed-effects model was used to combine the HR values. The pooled HR value was 1.67 (95 % CI 1.38–2.02; $P = 0.00$), with evidence of heterogeneity ($\chi^2 = 3.73$, $P = 0.59$, $I^2 = 0.0$ %), suggesting that CCND1 overexpression was associated with increased risk in ER-positive breast cancer patients (Fig 3).

CCND1 overexpression and neoadjuvant chemotherapy

In three studies containing 477 cases, the survival data (PFS and OS) were assessed for the impact of CCND1 overexpression on the prognosis of breast cancer patients who received epirubicin-based neoadjuvant chemotherapy.

A statistically significant risk of CCND1 overexpression in breast cancer was detected with an HR of 1.14 (95 %: 0.68–1.91; 0.63) and significant heterogeneity ($\chi^2 = 10.79$, $P = 0.01, I^2 = 81.5$ %), indicating that CCND1 overexpression had no impact on the PFS of patients who received epirubicin-based neoadjuvant chemotherapy. Similarly, there was no association between CCND1 overexpression and the OS of patients who received epirubicin-based neoadjuvant chemotherapy (HR 1.15, 95 % CI 0.79–1.66; $P = 0.47$). All of the results of subgroup survival analysis are shown in Table 2.

Publication bias

No publication bias was detected in our meta-analysis using Begg's and Egger's tests. Begg's funnel plots did not reveal any evidence of obvious asymmetry in this study. Fig 4a shows Begg's funnel plot of CCND1 overexpression for publication bias in terms of the OS of primary breast cancer patients. Furthermore, the P value of the Egger's test ($P = 0.76$) suggested no evidence of publication bias. The Begg's funnel plot of CCND1 overexpression for the publication bias of ER-positive breast cancer patients is shown in Fig 4b. Egger's test ($P = 0.80$) confirmed the results. Moreover, no publication bias was detected in the other sub-group meta-analyses.

Discussion

Cyclin D1, which regulates the G1/S transition, has been shown to accumulate at high levels in late G1 phase of the

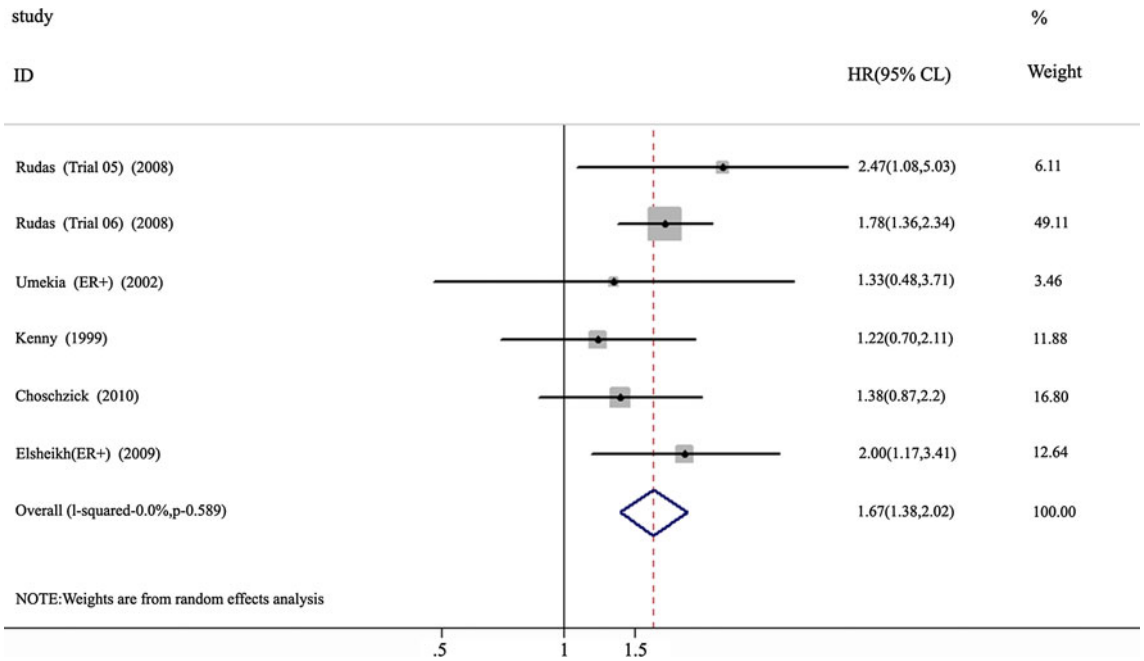

Fig. 3 A forest plot of the OS for ER-positive breast cancer patients

Table 2 The results of subgroup survival analysis

Subgroup	No. of studies	Cases/subjects	HR (95 % CI), *P* value	Model	Heterogeneity (χ^2, *P*, I^2)
OS in all studies	22	1654/4009	1.13 (0.87–1.47), 0.35	Random	57.55, 0.22, 63.5 %
PFS in all studies	11	1045/3685	1.25 (0.95–1.64), 0.12	Random	31.78, 0.00, 68.5 %
Methods					
OS in IHC	14	1121/2303	1.15 (0.84–1.57), 0.37	Random	38.33, 0.00, 66.1 %
OS in PCR	3	151/853	1.19 (0.41–3.46), 0.75	Random	7.62, 0.02, 73.8 %
Study design					
OS in retrospective	14	1175/2356	1.10(0.80–1.51), 0.57	Random	36.10, 0.00, 64.0 %
OS in cohort	5	272/1150	1.18(0.65–2.14), 0.59	Random	13.42, 0.01, 70.2 %
Analysis methods					
OS in UVA	14	1401/2702	1.01(0.73–1.41), 0.93	Random	39.18, 0.00, 66.8 %
OS in MVA	10	701/1827	1.51(1.03–2.22), 0.04	Random	23.41, 0.00, 61.6 %
Histology					
OS in IBC	8	720/1239	0.75(0.49–1.13), 0.17	Random	18.72, 0.01, 62.6 %
Region					
OS in Europe	10	735/2070	1.20(0.83–1.72), 0.34	Fixed	19.76, 0.02, 54.4 %
OS in Asia	7	625/1115	0.97(0.56–1.69), 0.92	Random	22.39, 0.00, 73.2 %
OS in the USA	3	192/446	1.45(0.75–2.78), 0.27	Random	7.62, 0.02, 73.8 %

No number, *OS* overall survival, *Random* random-effects model, *UVA* univariate analysis, *MVA* multivariate analysis, *IBC* invasive breast cancer, *Fixed* fixed-effects model

cell cycle. CCND1 overexpression has previously been reported to be associated with poor prognosis and tumor progression in several different tumor types, including breast cancer [39, 51, 52], because it can promote cell proliferation and differentiation by shortening the G1/S transition. However, no correlation was detected with the prognosis of unselected primary breast cancers in this meta-analysis. Furthermore, eight additional studies [39, 53–60] that were not included in this meta-analysis reported a negative correlation between CCND1 overexpression and the prognosis of breast cancer, although the detailed survival data of these studies are unavailable.

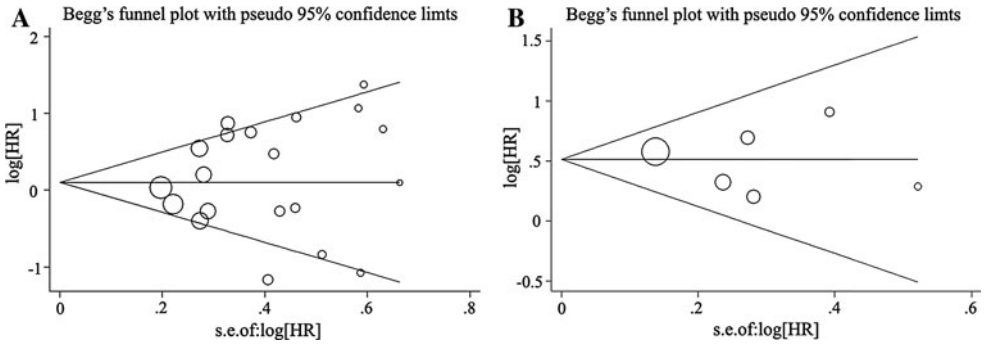

Fig. 4 A funnel plot for the OS of unselected primary breast cancers (**a**) and ER-positive breast cancer patients (**b**)

Nevertheless, the results of these studies support our finding that CCND1 overexpression has no impact on the prognosis of unselected primary breast cancers.

CCND1 gene amplification and CCND1 protein overexpression frequently occur in breast cancer, although protein overexpression is not always attributed to genetic amplification [39, 42, 43]. Nevertheless, Peurala et al. [24] showed that increased CCND1 protein levels were significantly correlated with increased mRNA expression. Moreover, the protein expression of CCND1 is believed to be more directly affected by CCND1 mRNA overexpression than CCND1 gene amplification [13]. These observations indicate that mechanisms other than genetic amplification are responsible for the altered CCND1 expression, such as ER status.

According to gene expression profiling by DNA microarray, breast cancer is divided into five main molecular classes [61–63]. These classes include basal-like breast cancers (ER-negative, progesterone receptor (PR)-negative, and HER2-negative tumors), HER2-positive cancers, normal breast-like, luminal-A cancers, which are mostly ER-positive, and histologically low-grade luminal-B cancers, which are also mostly ER positive, but might express low levels of hormone receptors, and are often high grade. In retrospective studies, the different genetic subtypes of breast cancer have exhibited different PFS and OS [64, 65]. The strong connection between CCND1 and ER status [14, 42, 44] implies that CCND1 might contribute to the prognosis of ER-positive patients.

In this meta-analysis, CCND1 overexpression was detected to serve as an independent predictor of poor prognosis in ER-positive breast cancer. CCND1 exhibited a strong correlation with ER-positive status in previous studies [14, 42, 44], confirming the important role of CCND1 in ER-positive breast cancer. Furthermore, CCND1 is induced by estrogen and growth factors, and it acts as a cellular sensor for their presence [66]. Thus, it might increase the competitive effect of tamoxifen, which has been proven to be an effective treatment in hormone receptor-positive breast cancer patients and ER-positive breast cancers [67].

Because the neoadjuvant chemotherapy regimens were not entirely consistent, the relationship between increased CCND1 expression and breast cancer patients with neoadjuvant chemotherapy needs to be validated in further studies.

Quality assessment according to REMARK guidelines was conducted for all 33 of the studies included in this meta-analysis. The studies included in this meta-analysis fulfilled, on average, 14 items (range from 10 to 18 items) of the guidelines. Sensitivity and sub-group analyses were performed to ensure that the results were reliable and valid. The rates of breast cancer incidence are reportedly higher in developed regions of the world (except Japan) than in most developing regions, such as eastern Africa [1]. However, there was no association between CCND1 overexpression and the prognosis of breast cancer in different regions. Invasive breast cancer is the most common pathological subtype of breast cancer. However, CCND1 overexpression was not an independent risk factor for invasive breast cancer. Moreover, we performed subgroup analysis according to the univariate or multivariate analyses used to evaluate the prognosis of breast cancer; the results exhibited no significant difference in either case. In summary, the results of the sensitivity and subgroup analysis revealed that no significant changes occurred in the results when poor-quality studies were excluded or in subgroup analyses.

As a meta-analysis, there are some limitations that should be discussed for further consideration. First, a meta-analysis based on individual patient data is the gold standard method. However, to our knowledge, it is rare for a meta-analysis to be based on individual patient data. Obtaining individual patient data for our studies was almost impossible. Therefore, we conducted a meta-analysis of the published literature. Second, a random-effects model was predominantly used for our analyses, except in the cases of ER-positive patients and MFS, due to their significant heterogeneity. Because the random-effects model reduced the effect of large samples with better quality, it was not as stable as the fixed-effects model. Third, certain reports with negative or controversial results

might not be reported, and therefore, publication bias is inevitable. Fourth, we conducted a literature search in the PubMed and EMBASE databases, and because we included articles that were published in English only, selection and language bias might exist. Last, the cutoff of methods used to assess ER overexpression was variable between studies, which might contribute in part to the observed heterogeneity.

Conclusion

In summary, CCND1 overexpression can serve as an independent prognostic indicator for poor prognosis in ER-positive breast cancer, but cannot distinguish patients with poor OS from groups with favorable prognosis (PFS, OS and MFS) in unselected primary breast cancers, and breast cancer patients with neoadjuvant chemotherapy.

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Conflict of interest The authors declare that they have no conflict of interest.

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