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Decoy Receptor 3 (DcR3) as a Biomarker of Tumor Deterioration in Female Reproductive Cancers: A Meta-Analysis

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

BCDEF 1 **Mengtong Jiang**
CF 2 **Xiaomiao Lin**
CF 3 **Rongquan He**
CF 3 **Xinggu Lin**
DF 1 **Lu Liang**
DF 1 **Ruixue Tang**
DF 1 **Dandan Xiong**
F 1 **Kanglai Wei**
DF 1 **Yiwu Dang**
F 1 **Zhenbo Feng**
ABDEG 1 **Gang Chen**

1 Department of Pathology, First Affiliated Hospital of Guangxi Medical University, Nanning, Guangxi, P.R. China
2 Department of Children Rehabilitation Medicine, Guangxi Maternal and Child Health Hospital, Nanning, Guangxi, P.R. China
3 Center of Genomic and Personalized Medicine, Guangxi Medical University, Nanning, Guangxi, P.R. China

Corresponding Author: Gang Chen, e-mail: chen_gang_triones@163.com

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Background: DcR3 (decoy receptor 3) has been proposed be involved in development and prognosis of female reproductive cancers, including cervical cancer, ovarian cancer, and breast cancer. The purpose of this meta-analysis was to explore the evidence for the correlation between DcR3 and the clinicopathological characteristics, as well as the overall survival time, in female reproductive cancers.





Material/Methods: Relevant studies were searched for in PubMed, Wiley Online Library, Web of Science, Science Direct, Cochrane Central Register of Controlled Trials, Google Scholar, EMBASE, Ovid, LILACS, Chinese CNKI, Chong Qing VIP, Wan Fang, and China Biology Medicine disc up to 30 September 2015. Data on the relationship between DcR3 expression and TNM stage, differentiation, lymph node metastasis, age, and overall survival time were extracted. Pooled odds ratios (ORs) and 95% CIs (confidence intervals) were estimated by forest plot.

Results: Twelve studies with 1127 patients met the inclusion criteria for this meta-analysis. Overexpression of DcR3 was significantly related to the risk of female reproductive cancers (OR=10.69, 95% CI: 6.33–18.05), TNM stage (OR=5.51, 95% CI: 2.83–10.71), differentiation (OR=4.16, 95% CI: 2.28–7.60), lymph node metastasis (OR=5.89, 95% CI: 3.16–10.9), age (OR=0.85, 95% CI: 0.51–1.44), and overall survival time (OR=1.84, 95% CI: 0.58–5.83). Subgroup analyses showed that overexpression of DcR3 in cervical, ovarian, and breast cancer all had similar relationships with these clinicopathological parameters.

Conclusions: Our meta-analysis suggests that overexpression of DcR3 may play vital roles in the tumorigenesis and deterioration of female reproductive cancers. However, the relationship between DcR3 expression and prognosis needs further investigation.

MeSH Keywords: **Genes, Neoplasm • Genital Diseases, Female • Meta-Analysis • Prognosis • Receptors, Tumor Necrosis Factor, Member 6b • Survival Analysis**

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Background

Decoy receptor 3 (DcR3) – also referred to as TR6, M68, or TNFRSF6B – is a family member of the tumor necrosis factor receptor (TNFR) superfamily. DcR3 acts as a binding partner in multiple apoptotic ligands inhibiting apoptosis. DcR3 has been described in many malignant tumors, such as gastric [1], hepatocellular [2], colon [3], lung [4], cervical [5], ovarian [6], and breast cancer [7]. A gastrointestinal cancer meta-analysis [8] reported that overexpression of DcR3 was closely related with clinicopathological features, including TNM stage, grade of differentiation, lymph node metastasis, infiltration degree, and distant metastasis. The present study is the only meta-analysis on the relationship between DcR3 and malignancies.

Female reproductive cancers are among the most common causes of cancer-related death, including breast cancer, ovarian cancer, uterine corpus cancer, and cervical cancer. Some genes and molecules are particularly useful as tracking, identifying, and validating biomarkers for diagnosis and treatment of female reproductive cancers [9–11]. Although some studies have explored the role of DcR3 overexpression in cervical cancer, ovarian cancer, and breast cancer, there is still no summary evidence for the association between DcR3 and overall female reproductive cancers. Therefore, we conducted the present meta-analysis to explore the relation between the level of DcR3, clinicopathological characteristics, and survival of female reproductive cancer patients.

Material and Methods

Search strategy and data extraction

PubMed, Wiley Online Library, Web of Science, Science Direct, Cochrane Central Register of Controlled Trials, Google Scholar, EMBASE, Ovid, LILACS, Chinese CNKI, Chong Qing VIP, Wan Fang, and China Biology Medicine disc were searched up to 30 September 2015 with a random combination of the terms: ‘DcR3 or TR6 or M68 or TNFRSF6B’, ‘cervical or ovarian or ovary or oophoro* or uterine or breast or endometrial or choriocarcinoma or fallopian tube’ and ‘cancer or tumor or carcinoma or neoplas* or malignan*’. All of the relevant literature, including review articles and potential references, were searched for additional pertinent studies. Articles were searched and screened by 2 investigators independently. In the meta-analysis, studies that met the following criteria were eligible: (1) Patients in studies were clearly diagnosed with cervical cancer, ovarian cancer, or breast cancer, as well as other female reproductive cancers; (2) Studies included were case-control studies and evaluated the relationship between DcR3 expression and clinicopathological features or prognosis in female reproductive cancers; (3) The definition of DcR3-positive was

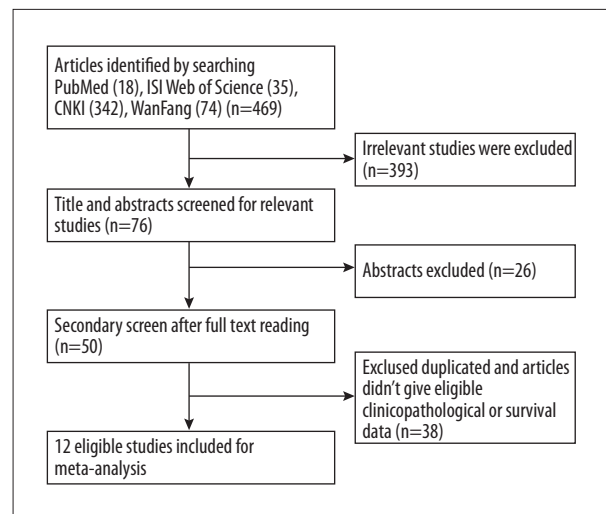


Figure 1. Flow diagram of study identification.

tested by immunohistochemistry (IHC) method; (4) Sufficient information of the correlation of DcR3 with clinicopathological features or overall survival time was provided to estimate odds ratio (OR) and hazard ratio (HR); and (5) Articles were written in English or Chinese. Letters, reviews, conference abstracts, and duplicated studies were excluded. Two reviewers screened all information independently to exclude irrelevant studies. Disagreements were resolved by a third reviewer. Two independent reviewers read full texts of all eligible studies and extracted relevant data, including author, year, country, cancer type, patient number, test method, clinicopathological parameters (age, TNM stage, grade of differentiation, and lymph node metastasis), and overall survival time.

Statistics

Stata 12.0 was used for statistical analysis. ORs with 95% confidence intervals (CIs) were calculated with a forest plot. The heterogeneity between the studies was evaluated by I^2 test. According to the results of heterogeneity analysis, a random-effects model was used. Potential causes of statistical heterogeneity were explored by subgroup analysis. The software Engauge Digitizer 4.1 was used to extract the survival data from a K-M curve in some articles. Publication bias was analyzed by Begg's funnel plot test. $P < 0.05$ was considered statistically significant.

Results

Eligible studies

With the aforementioned search strategies, 469 articles were retrieved initially. Of these, 393 were excluded after reviewing the titles and abstracts because these articles described

Table 1. Characteristics of studies included in the meta-analysis.

No.	Year	Author	Country	Organ	Number	Expression	Age	TNM	Differentiation	Lymph node metastasis	Overall survival time (month)
						Cancer (+/-) Control (+/-)	Old (+/-) Young (+/-)	3,4 (+/-) 1,2 (+/-)	Low (+/-) High (+/-)	Metastasis (+/-) Non-metastasis (+/-)	
1	2013	Gao SS [5]	China	Cervical	84	36/6 15/27	NA	NA	NA	NA	NA
2	2012	Lu JH [12]	China	Cervical	101	27/3 37/34	NA	NA	NA	NA	NA
3	2011	Cao YX [13]	China	Cervical	93	42/15 10/26	14/3 21/2	28/11 8/12	15/2 22/18	10/0 11/8	(+) 66.10±2.78 (-) 77.79±2.22
4	2013	Wang ZR [14]	China	Cervical	75	29/11 10/25	20/24 9/7	15/1 14/10	12/0 17/11	9/1 7/11	NA
5	2008	Joseph P [15]	America	Ovarian	44	4/0 18/22	NA	NA	21/19 1/3	NA	Median: (+) 31 (-) 36
6	2015	Cheng L [6]	China	Ovarian	153	77/9 15/52	49/3 28/6	56/2 21/7	52/2 25/7	48/2 29/7	Median: (+) 31 (-) 46
7	2009	Wang JO [16]	China	Ovarian	106	44/27 7/28	6/3 35/14	21/3 20/14	21/4 20/13	NA	NA
8	2011	Gao HH [17]	China	Breast	82	24/17 10/31	NA	7/1 17/16	NA	17/4 7/13	NA
9	2005	Wang LP [7]	China	Breast	53	18/11 0/4	NA	NA	NA	14/6 4/5	NA
10	2007	Shan GP [18]	China	Breast	74	25/16 0/33	11/8 13/8	6/2 19/14	11/5 14/11	20/7 5/9	NA
11	2010	Chen G [19]	China	Breast	136	58/21 0/57	32/13 26/8	51/6 7/15	29/1 29/20	32/1 26/20	NA
12	2014	Wu QW [20]	China	Breast	126	58/5 34/29	17/1 41/4	5/1 53/4	30/2 23/3	28/2 30/3	NA

non-human experiments or other cancer types. Then, due to duplication or no report of any relevant outcomes, 26 of the remaining articles were excluded (Figure 1). Finally, a total of 12 eligible studies [5–7,12–20] with 1127 participants were included in this meta-analysis. The characteristics of all 12 articles are summarized in Table 1. The test method of all included studies was only IHC.

Meta-analysis

In this meta-analysis, we assessed the correlation between DcR3 expression and cancer risk, clinicopathological features, and overall survival time of patients with female reproductive cancers. As shown in Figure 2, overexpression of DcR3 was associated with female reproductive cancer risk (OR=10.69, 95% CI: 6.33–18.05). Furthermore, subgroup analysis showed a consistent trend; for example, cervical cancer (OR=7.97, 95% CI: 4.70–13.49), ovarian cancer (OR=14.03, 95% CI: 3.16–62.01), and breast cancer (OR=19.35, 95% CI: 4.46–84.03).

In analysis of female reproductive cancer patients regardless of subtype, 3 clinicopathological parameters were found to

be significantly associated with overexpression of DcR3 as compared to controls: advanced TNM stage (OR=5.51, 95% CI: 2.83–10.71), poor grade of differentiation (OR=4.16, 95% CI: 2.28–7.60), and lymph node metastasis (OR=5.89, 95% CI: 3.16–10.96).

In the sub-analysis, a stronger association was found between TNM stage and patients with overexpression of DcR3 in ovarian cancer (OR=6.80, 95% CI: 2.50–18.50) than in cervical cancer (OR=4.76, 95% CI: 1.74–13.01) or breast cancer (OR=3.73, 95% CI: 0.73–19.09, Figure 3).

As shown in Figure 4, for each type of cancer, a concordant relationship was also observed between DcR3 expression and grade of differentiation: cervical cancer (OR=7.70, 95% CI: 1.89–31.38), ovarian cancer (OR=4.32, 95% CI: 1.71–10.92), and breast cancer (OR=3.56, 95% CI: 0.79–16.00).

In sub-analysis of association between patients with different cancers with overexpression of DcR3 and lymph node metastasis, cervical cancer had the highest rank (OR=14.64, 95% CI: 2.41–89.04), ovarian cancer was second (OR=5.79, 95% CI:

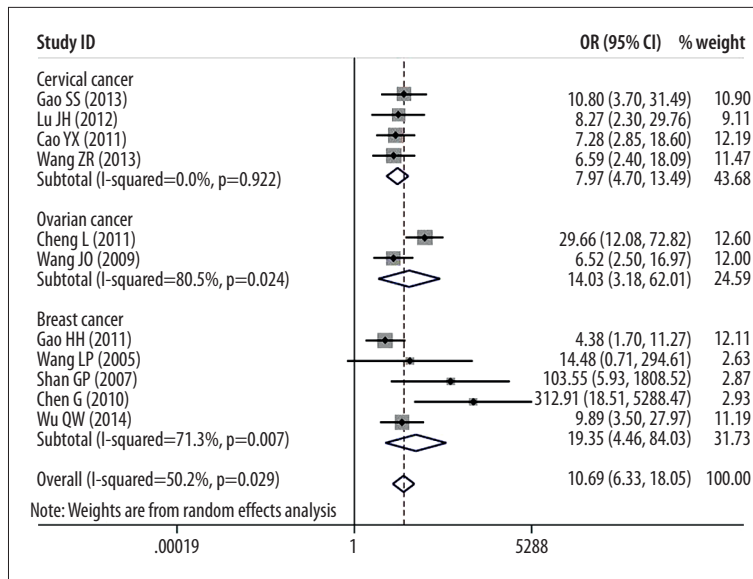


Figure 2. Forest plot of odds ratios (ORs) with corresponding 95% CIs for the association of DcR3 expression with female reproductive cancers risk.

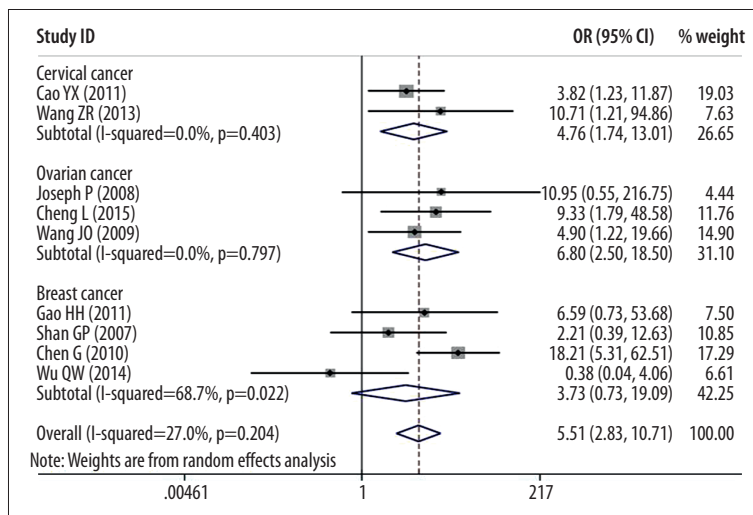


Figure 3. Forest plot of odds ratios (ORs) with corresponding 95% CIs for the association of DcR3 expression with TNM stages.

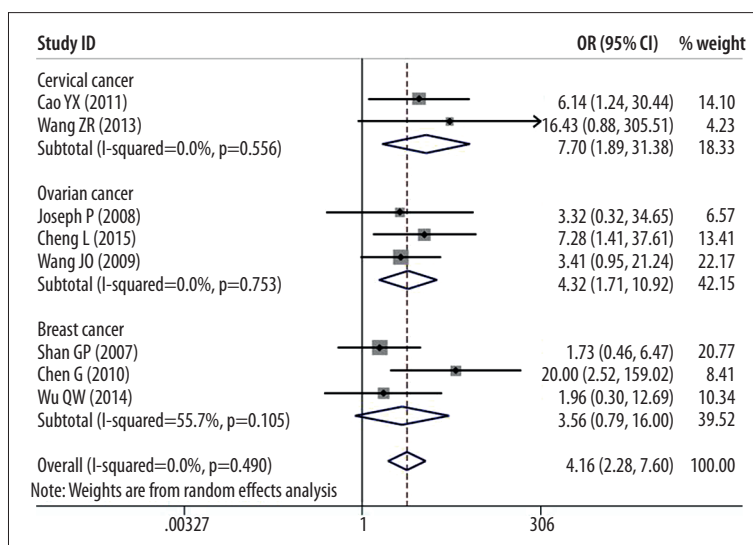


Figure 4. Forest plot of odds ratios (ORs) with corresponding 95% CIs for the association of DcR3 expression with differentiation.

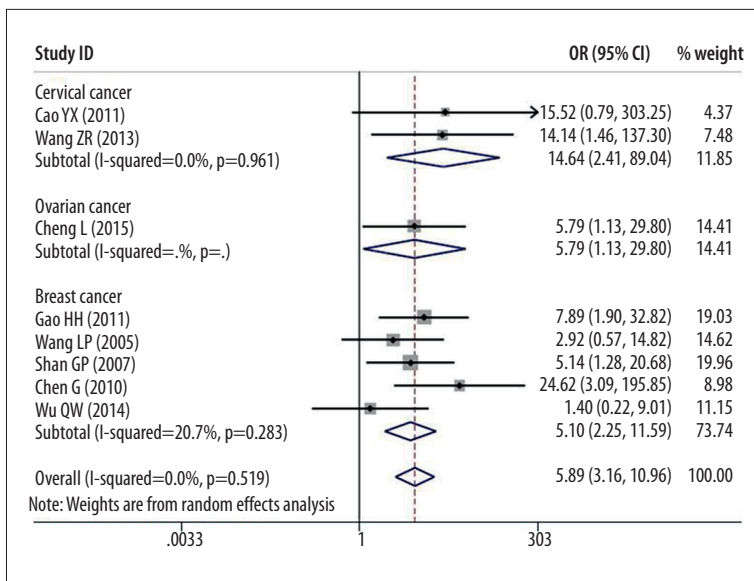


Figure 5. Forest plot of odds ratios (ORs) with corresponding 95% CIs for the association of DcR3 expression with lymph node metastasis.

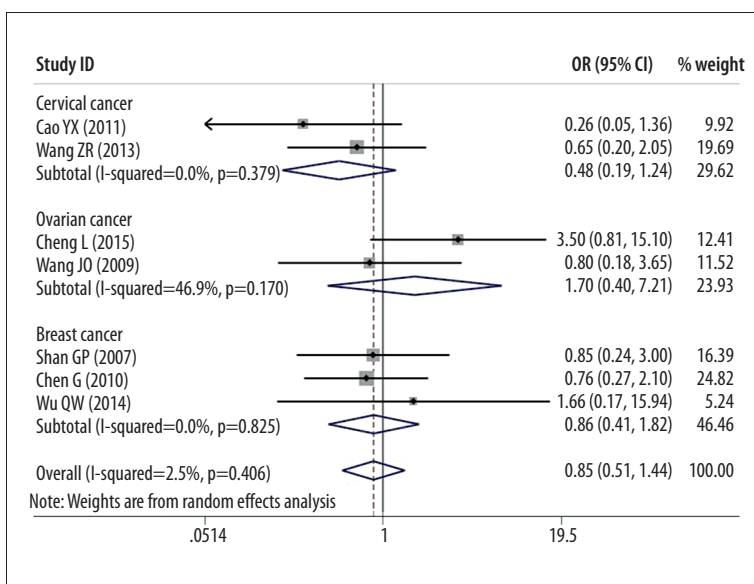


Figure 6. Forest plot of odds ratios (ORs) with corresponding 95% CIs for the association of DcR3 expression with age.

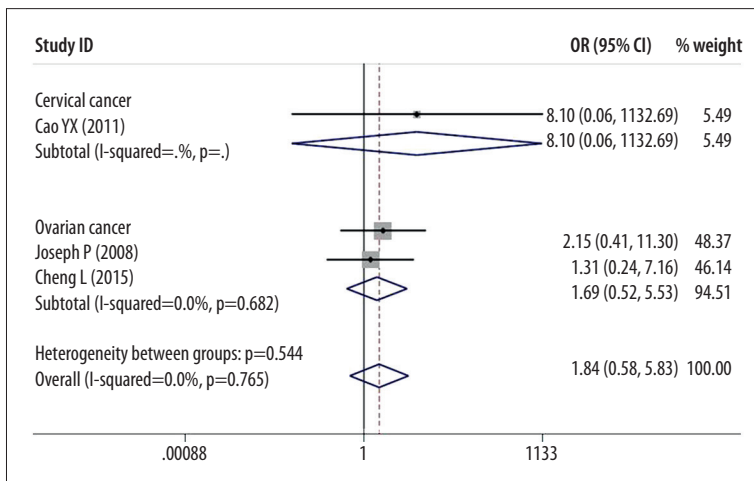


Figure 7. Forest plot of odds ratios (ORs) with corresponding 95% CIs for the association of DcR3 expression with overall survival time.

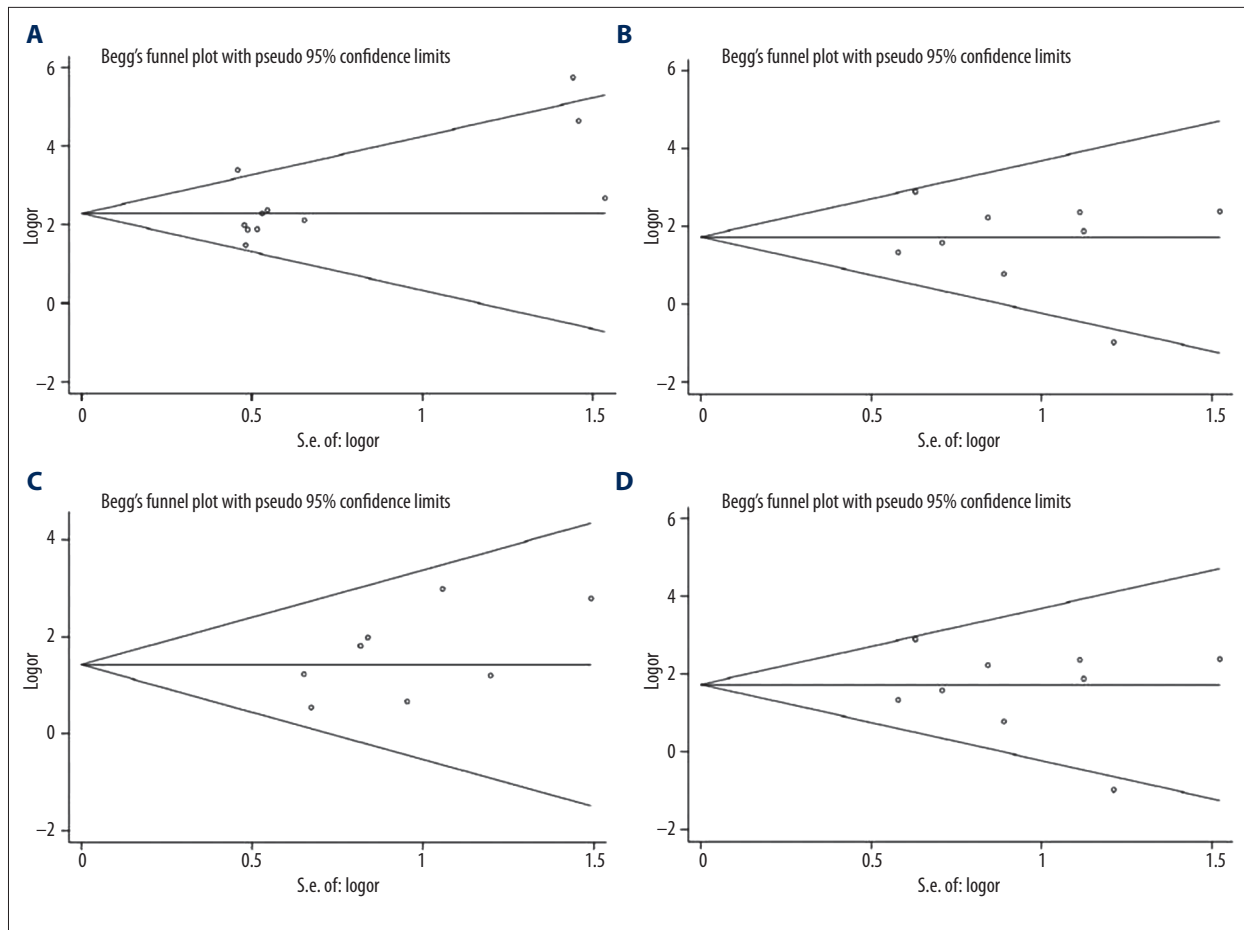


Figure 8. (A) Begg's publication bias plot of publication bias for studies regarding overexpressed DcR3 and female reproductive cancers risk in the meta-analysis. (B) Begg's publication bias plot of publication bias for studies regarding overexpressed DcR3 and TNM stage in the meta-analysis. (C) Begg's publication bias plot of publication bias for studies regarding overexpressed DcR3 and differentiation in the meta-analysis. (D) Begg's publication bias plot of publication bias for studies regarding overexpressed DcR3 and lymph node metastasis in the meta-analysis.

1.13–29.80), and breast cancer was third (OR=5.10, 95% CI: 2.25–11.59) (Figure 5) (all $P < 0.05$).

However, as shown in Figures 6 and 7, there was no association between DcR3 overexpression and the age of female reproductive cancer patients (OR=0.85, 95% CI: 0.51–1.44, $P=0.554$) or overall survival time (OR=1.84, 95% CI: 0.58–5.83, $P=0.300$).

Publication bias

As shown in Figure 8, Begg's test suggested that there was no publication bias for risk of female reproductive cancers ($P=0.097$), TNM stage ($P=0.559$), grade of differentiation ($P=0.156$), lymph node metastasis ($P=0.345$), age ($P=0.685$), or overall survival time ($P=0.394$).

Discussion

Overexpression of DcR3 has been found in many malignant tumors, but, as reported, DcR3 overexpression could not be detected in non-tumor tissues. Studies have shown that DcR3 regulates the activity and differentiation of immune cells, and regulates apoptosis. Therefore, DcR3 may be involved in invasion and metastasis of tumor cells [18]. There are at least 5 possible specific mechanisms involved. First, DcR3 can act as a functional FasL decoy receptor that can bind to Fas ligand (FasL) and inhibit tumor cell killing [21,22]. Second, DcR3 might promote tumor growth by attenuating the Th1 response and suppressing cell-mediated immunity [23–25]. Third, DcR3.Fc (DcR3 fusion protein with immunoglobulin Fc) is able to modulate the expression of a few macrophage markers, including CD14, CD16, CD64, and human leukocyte antigen-DR, suggesting that DcR3 Fc might have potent, suppressive effects in down-regulating the host-immune system [26–28]. Fourth,

DcR3 can inhibit stromal cell-derived factor 1 chemotaxis of T lymphocytes, thus reducing the organization of CD4+ and CD8+ T lymphocyte infiltration [29]. Fifth, DcR3 induces the apoptosis of dendritic cell (DC) via activating PKC-delta and JNK, then up-regulates DR5 to recruit Fas-associated death domain (FADD) to propagate the apoptotic signals [30,31]. The functions and mechanisms might not be completely the same in these 3 types of female reproductive cancers.

In breast cancer, DcR3 may be regarded as a negative regulator of cancer aggressiveness during development and progression of certain types of breast cancer by using anti-DcR3 monoclonal antibody and anti-DcR3 hammerhead ribozyme transgenes in breast cancer cells [32,33]. Studies have reported that lymphatic microvessel density (LMVD) was elevated in the cancer tissue and lymph node with metastasis, and DcR3 may promote lymph node metastasis of breast cancer by inducing the formation of new lymphatic vessels and increasing opportunities for lymph node metastasis [17,20]. Wang et al. [7] reported that after the treatment of DcR3 neutralized with DcR3 antibody, the effect on proliferation of breast cancer cell line was decreased, while addition of Fas-L and DcR3 enhanced proliferation. One of the main mechanisms may be that DcR3 blocks the Fas-L-induced apoptosis.

In cervical cancer, Peyre et al. [34] reported that the number of T cells was significantly lower in peripheral blood of cervical cancer patients, and there was an obvious negative correlation between DCR3 expression and CD3+, CD4+/CD8+T in peripheral blood. Therefore, they presumed that DCR3 is related to tumor immune escape in patients with cervical cancer. The expression and distribution of T cells in local tissues of cervical cancer can reflect immune status in the body.

In ovarian cancer, Lin et al. [35] reported that the proliferation of CAOV3 cells was significantly decreased by DcR3 siRNA in comparison with the normal control group and negative control group, indicating that DcR3 siRNA can inhibit the proliferation of ovarian cancer cell line CAOV3 by recognizing and degrading DcR3 mRNA. It has been reported that DcR3 is expressed by epithelial ovarian cancers, concentrated in ascites, and ovarian cancer with high levels of DcR3 is associated with Fas-L-induced apoptosis and platinum resistance [15,36].

Several clinicopathological characteristics are known to be associated with poor prognosis, including large tumor size, advanced tumor stage, poor differentiation, deep invasion, lymph node metastasis, perineural invasion, and lymphatic and vascular invasion [37–41]. A previous meta-analysis [8] reported that overexpression of DcR3 was closely related with some clinicopathological features, including TNM stage, grade of differentiation, lymph node metastasis, infiltration degree, and metastasis in gastrointestinal cancer. Some researchers have

reported close correlations between DcR3 expression and prognosis of female reproductive cancer, but no clear evidence was provided. Our analysis suggests that overexpression of DcR3 is related to risk of female reproductive cancer, advanced TNM stage, poor differentiation, and worse lymph node metastasis. After subgroup analysis, overexpression of DcR3 in cervical cancer, ovarian cancer, and breast cancer all had a consistent relationship with these clinicopathological parameters.

To the best of our knowledge, the present meta-analysis is the first to explore the potential relationship between DcR3 expression and female reproductive cancers. However, our study has some limitations. First, we only included 12 studies (including 1127 female reproductive cancers patients), in which just 3 studies (including 290 female reproductive cancers patients) investigated the correlation between DcR3 expression and overall survival time. Therefore, the association of DcR3 expression with overall survival time still needs to be studied in a larger number of samples. Second, there could be potential country bias in our meta-analysis, because only 1 study was performed in the USA, and the patients in the other 11 studies were Chinese. Third, although we aimed to study the relationships between DcR3 expression and all female reproductive cancers, only 3 types of female reproductive cancers were recently eligible: cervical, ovarian, and breast cancer. We will continue to study the relationship between DcR3 expression and other female reproductive cancer types, such as ovary, endometrial, choriocarcinoma, and fallopian tube cancer, and we will update our meta-analysis accordingly.

Conclusions

Our meta-analysis indicates a positive association between the overexpression of DcR3 and carcinogenesis, deterioration, and progression of female reproductive cancers. In conclusion, female productive cancer risk is strongly dependent on overexpression of DcR3, and DcR3 may be used as a biomarker to predict unfavorable cancer prognosis. In addition, our group has previously proved that DcR3 neutralizing antibodies can suppress cell growth and induce apoptosis in glioma cells [42,43], which suggests that DcR3 could be a target in molecular therapy in cancers, including female reproductive cancers.

Statement

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Conflicts of interest

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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