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

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Source of support:
This study was supported partly by the Fund of Guangxi Natural Scientific Research (No. 2015GXNSFAA139187) and Research Fund of Guangxi Bureau of Health (Z2014057)

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

Full-text PDF: http://www.medscimonit.com/abstract/index/idArt/896226
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 [8]. 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 malignant*’. 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 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 I² 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
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 in-
cluded in this meta-analysis. The characteristics of all 12 arti-
cles are summarized in Table 1. The test method of all includ-
est 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 as-
associated with female reproductive cancer risk (OR=10.69, 95%
CI: 6.33–18.05). Furthermore, subgroup analysis showed a con-
sistent 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 ovar-
ian 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: 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).

As shown in Figure 4, for each type of cancer, a concordant
relationship was also observed between DcR3 expression and
differentiation; cervical cancer (OR=7.70, 95% CI:
2.28–7.60), and lymph node metastasis (OR=5.89, 95% CI:
3.16–10.96).

In sub-analysis of association between patients with different
cancers with overexpression of DcR3 and lymph node meta-
stasis, cervical cancer had the highest rank (OR=14.64, 95%
CI: 6.33–31.38), ovarian cancer (OR=4.32, 95% CI: 1.71–10.92),
and breast cancer (OR=3.56, 95% CI: 0.79–16.00).

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

| No. | Year | Author | Country | Organ | Expression | Cancer (+/–) | Control (+/–) | Age | Old (+/–) | Young (+/–) | TNM | 3,4 (+/–) | 1,2 (+/–) | Differentiation | Low (+/–) | High (+/–) | Lymph node metastasis | Metastasis (+/–) | Non-metastasis (+/–) | Overall survival time (month) |
|-----|------|--------|---------|-------|------------|-------------|--------------|-----|----------|------------|-----|----------|--------|-----------------|---------|----------|----------------------|------------------|---------------------|------------------------|
| 1   | 2013 | Gao SS | China   | Cervical | 84        | 36/6        | NA           | NA  | NA       | NA         | NA  | NA       | NA     | NA              | NA      | NA       | NA                   | NA               | NA                  |
| 2   | 2012 | Lu JH  | China   | Cervical | 101       | 27/3        | 15/28        | NA  | NA       | NA         | NA  | NA       | NA     | NA              | NA      | NA       | NA                   | NA               | NA                  |
| 3   | 2011 | Cao YX | China   | Cervical | 93        | 42/15       | 8/28         | 14/15| 2/15     | 1/5         | NA  | NA       | NA     | NA              | NA      | NA       | NA                   | NA               | NA                  |
| 4   | 2013 | Wang ZR| China   | Cervical | 75        | 29/11       | 15/20        | 20/24| 9/7      | 7/10        | NA  | NA       | NA     | NA              | NA      | NA       | NA                   | NA               | NA                  |
| 5   | 2008 | Joseph P | America | Ovarian | 44        | 4/0         | 2/19         | NA  | NA       | NA         | NA  | NA       | NA     | 21/19          | NA      | Median: (+) 31 | Median: (+) 31     | NA               | (-) 36              |
| 6   | 2015 | Cheng L | China   | Ovarian  | 153       | 77/9        | 28/6         | 49/3 | 7/8      | 15/2        | NA  | NA       | NA     | 7/16          | NA      | 17/4     | NA                   | NA               | NA                  |
| 7   | 2009 | Wang JO | China   | Ovarian  | 106       | 44/27       | 21/3         | 27/26| 12/7     | 12/14       | NA  | NA       | NA     | 10/14         | NA      | 20/14    | NA                   | NA               | NA                  |
| 8   | 2011 | Gao HH | China   | Breast   | 82        | 24/17       | 7/1          | 17/16| NA       | NA         | NA  | NA       | NA     | 17/4          | NA      | 7/13     | NA                   | NA               | NA                  |
| 9   | 2005 | Wang LP | China   | Breast   | 53        | 18/11       | 0/2          | NA  | NA       | NA         | NA  | NA       | NA     | 14/6          | NA      | 4/5      | NA                   | NA               | NA                  |
| 10  | 2007 | Shan GP | China   | Breast   | 74        | 25/16       | 6/2          | 11/8 | 6/2      | 17/10       | NA  | NA       | NA     | 19/14         | NA      | 20/7     | NA                   | NA               | NA                  |
| 11  | 2010 | Chen G  | China   | Breast   | 136       | 58/21       | 29/2        | 32/13| 26/8     | 12/14       | NA  | NA       | NA     | 29/1          | NA      | 29/20    | NA                   | NA               | NA                  |
| 12  | 2014 | Wu QW  | China   | Breast   | 126       | 58/5        | 5/1          | 17/1 | 41/4     | 17/20       | NA  | NA       | NA     | 30/2          | NA      | 28/2    | NA                   | NA               | NA                  |
### Figure 2. Forest plot of odds ratios (ORs) with corresponding 95% CIs for the association of DcR3 expression with female reproductive cancers risk.

| Study ID | OR (95% CI) | % weight |
|----------|-------------|----------|
| Cervical cancer | 10.80 (3.70, 31.49) | 10.90 |
| Gao SS (2013) | 8.27 (2.30, 29.76) | 9.11 |
| Lu JH (2012) | 7.28 (2.85, 18.60) | 12.19 |
| Cao YX (2011) | 6.59 (2.40, 18.09) | 11.47 |
| Wang ZR (2013) | 7.97 (4.70, 13.49) | 43.68 |
| Ovarian cancer | 29.66 (12.08, 72.82) | 12.60 |
| Cheng L (2011) | 6.52 (2.50, 16.97) | 12.00 |
| Wang JO (2009) | 14.03 (3.18, 62.01) | 24.59 |
| Breast cancer | 10.90 | 10.80 (3.70, 31.49) |
| Gao HH (2011) | 8.27 (2.30, 29.76) |
| Wang LP (2005) | 7.28 (2.85, 18.60) |
| Shan GP (2007) | 6.59 (2.40, 18.09) |
| Chen G (2010) | 7.97 (4.70, 13.49) |
| Wu QW (2014) | 10.80 (3.70, 31.49) |
| Overall (I-squared=50.2%, p=0.029) | 10.69 (6.33, 18.05) | 100.00 |

Note: Weights are from random effects analysis

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

| Study ID | OR (95% CI) | % weight |
|----------|-------------|----------|
| Cervical cancer | 3.82 (1.23, 11.87) | 19.03 |
| Gao SS (2013) | 10.71 (1.21, 94.86) | 7.63 |
| Wang ZR (2013) | 4.76 (1.74, 13.01) | 26.65 |
| Ovarian cancer | 10.95 (0.55, 216.75) | 4.44 |
| Joseph P (2008) | 9.33 (1.79, 48.58) | 11.76 |
| Cheng L (2015) | 4.90 (1.22, 19.66) | 14.90 |
| Wang JO (2009) | 6.80 (2.05, 21.30) | 31.10 |
| Breast cancer | 6.59 (0.73, 53.68) | 7.50 |
| Gao SS (2013) | 2.21 (0.39, 12.63) | 10.85 |
| Wang ZR (2013) | 18.21 (5.31, 62.51) | 17.29 |
| Overall (I-squared=50.2%, p=0.029) | 5.51 (2.83, 10.71) | 100.00 |

Note: Weights are from random effects analysis

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

| Study ID | OR (95% CI) | % weight |
|----------|-------------|----------|
| Cervical cancer | 6.14 (1.24, 30.44) | 14.10 |
| Gao SS (2013) | 16.43 (0.88, 305.51) | 4.23 |
| Wang ZR (2013) | 7.70 (1.89, 31.38) | 18.33 |
| Ovarian cancer | 10.95 (0.55, 216.75) | 4.44 |
| Joseph P (2008) | 3.32 (0.32, 34.65) | 6.57 |
| Cheng L (2015) | 7.28 (1.41, 37.61) | 13.41 |
| Wang JO (2009) | 3.41 (0.95, 12.69) | 22.17 |
| Breast cancer | 1.73 (0.46, 6.47) | 20.77 |
| Shan GP (2007) | 20.00 (2.52, 159.02) | 8.41 |
| Chen GP (2010) | 1.96 (0.30, 12.69) | 10.34 |
| Wu QW (2014) | 3.56 (0.79, 16.00) | 39.52 |
| Overall (I-squared=0.0%, p=0.490) | 4.16 (2.28, 7.60) | 100.00 |

Note: Weights are from random effects analysis
Forest plot of odds ratios (ORs) with corresponding 95% CIs for the association of DcR3 expression with lymph node metastasis.

### Study ID

| OR (95% CI) | % weight |
|-------------|----------|
| Cervical cancer |
| Cao YX (2011) | 15.52 (0.79, 303.25) | 4.37 |
| Wang ZR (2013) | 14.44 (1.86, 113.01) | 7.48 |
| Subtotal (I-squared=0.0%, p=0.961) | 14.64 (2.41, 89.04) | 11.85 |
| Ovarian cancer |
| Cheng L (2015) | 5.79 (1.13, 29.80) | 14.41 |
| Subtotal (I-squared=0.0%, p=0.519) | 5.79 (1.13, 29.80) | 14.41 |
| Breast cancer |
| Gao HH (2011) | 7.89 (1.90, 32.82) | 19.03 |
| Wang LP (2005) | 2.92 (0.57, 14.82) | 14.62 |
| Shan GP (2007) | 5.14 (1.20, 20.68) | 19.96 |
| Chen G (2010) | 24.62 (3.09, 195.85) | 8.98 |
| Wu QW (2014) | 1.40 (0.22, 9.01) | 11.15 |
| Subtotal (I-squared=20.7%, p=0.283) | 5.10 (2.25, 11.59) | 73.74 |
| Overall (I-squared=0.0%, p=0.519) | 5.89 (3.16, 10.96) | 100.00 |

Note: Weights are from random effects analysis.

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

### Study ID

| OR (95% CI) | % weight |
|-------------|----------|
| Cervical cancer |
| Cao YX (2011) | 0.26 (0.05, 1.36) | 9.92 |
| Wang ZR (2013) | 0.65 (0.20, 2.05) | 19.69 |
| Subtotal (I-squared=0.0%, p=0.379) | 0.48 (0.10, 2.24) | 29.62 |
| Ovarian cancer |
| Cheng L (2015) | 3.50 (0.81, 15.10) | 12.41 |
| Wang J0 (2009) | 0.80 (0.18, 3.65) | 11.52 |
| Subtotal (I-squared=46.9%, p=0.283) | 1.70 (0.40, 7.21) | 23.93 |
| Breast cancer |
| Shan GP (2007) | 0.85 (0.24, 3.00) | 16.39 |
| Chen G (2010) | 0.76 (0.27, 2.10) | 24.82 |
| Wu QW (2014) | 1.66 (0.17, 15.94) | 5.24 |
| Subtotal (I-squared=0.0%, p=0.406) | 0.86 (0.41, 1.82) | 46.46 |
| Overall (I-squared=2.5%, p=0.406) | 0.85 (0.51, 1.44) | 100.00 |

Note: Weights are from random effects analysis.

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

### Study ID

| OR (95% CI) | % weight |
|-------------|----------|
| Cervical cancer |
| Cao YX (2011) | 8.10 (0.06, 1132.69) | 5.49 |
| Subtotal (I-squared=0.0%, p=..) | 8.10 (0.06, 1132.69) | 5.49 |
| Ovarian cancer |
| Joseph P (2008) | 2.15 (0.41, 11.30) | 48.37 |
| Cheng L (2015) | 1.31 (0.24, 7.16) | 46.14 |
| Subtotal (I-squared=0.0%, p=0.682) | 1.69 (0.32, 5.53) | 94.51 |
| Heterogeneity between groups: p=0.544 | 1.84 (0.58, 5.83) | 100.00 |
| Overall (I-squared=0.0%, p=0.765) | 1.84 (0.58, 5.83) | 100.00 |

Note: Weights are from random effects 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 clinical 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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