Copy number variation and high expression of DNA topoisomerase II alpha predict worse prognosis of cancer: a meta-analysis

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Abstract

**Background:** Increasing numbers of literatures have investigated the association between TOP2A and cancer prognosis. But the results of the relationship between the two were inconclusive. The aim of this meta-analysis was to elucidate whether TOP2A could predict prognosis of cancer.

**Materials and Methods:** A systematically searching for potentially valuable literature was conducted through electronic databases containing PubMed and Web of Science. Hazard Ratio (HR) and their 95% confidence interval (CI) were used to assess the strength of association between TOP2A and cancer prognosis.

**Results:** Finally twenty-five studies were included in this meta-analysis. High expression of TOP2A was associated with shorter disease free survival (DFS) of cancer prognosis compared with low expression of TOP2A (HR= 1.36, 95% CI= 1.18-1.57, P<0.001). Amplification of TOP2A gene showed no significant association with overall survival (OS), disease free survival (DFS) or relapse free survival (RFS) compared with non-amplification of TOP2A (OS: HR= 0.96, 95%CI= 0.75-1.22, P= 0.735; DFS: HR= 0.93, 95%CI= 0.70-1.23, P= 0.621; RFS: HR= 0.97, 95%CI= 0.71-1.34, P= 0.867). In the subgroup of regions, TOP2A amplification was associated with longer overall survival (HR= 0.66, 95%CI= 0.46-0.96, P= 0.029) in Australia. Alteration (amplification or deletion) of TOP2A gene demonstrated shorter survival according to OS and RFS compared with those with normal TOP2A status (OS: HR= 1.37, 95%CI= 1.22-1.55, P<0.001; RFS: HR= 1.26, 95%CI= 1.12-1.41, P<0.001).

**Conclusion:** High TOP2A expression suggested significant relationship with worse cancer prognosis. Alteration (amplification or deletion) of TOP2A gene was also significantly related to shorter survival of cancer patients. Therefore, TOP2A might be used as an indicator for poor prognosis of cancer in the future.

Key words: TOP2A, cancer, copy number variation, prognosis.

Introduction

Malignant tumor, characterized by strengthened and unlimited cell division during the cellular genetic process [1], is the leading cause of death in the world. As the genetic material inside every cell nucleus, DNA is indispensable for the maintenance of genetic stability and integrity. Because of the structure of duplex DNA, it inevitably leads the consequences of the topology such as supercoils [2]. DNA topoisomerases, ubiquitously present in eukaryotes, archaeabacteria and Eubacteria, are necessary for the regulation of DNA topology in various cellular procedures [3, 4]. A number of studies have indicated that DNA topoisomerases play an essential role in the DNA world through allowing DNA double helices or strands to cut across each other [4, 5]. According to their different acting mechanisms, DNA topoisomer-
ases can be classified as type I and type II enzymes [3, 6]. TOP2A is one of the isoenzymes which can mediate the catalytic activity of type II topoisomerases [6].

TOP2A (DNA topoisomerase II alpha) gene, mapped to chromosome 17q12-q21, covers approximately 27.5 kb and includes 35 exons, encoding a 170 kDa protein [7]. TOP2A encodes an enzyme which is implicated in almost any process of DNA metabolism including transcription, replication, movement and untangling [3, 8, 9], which catalyze the passage of two DNA duplexes across each other to resolve the entanglements and coiling of cellular DNA [10]. It modulates the topological states of DNA by transient cleavage, strand passing and religation of double-stranded DNA resulting in decatenation of intertwined DNA molecules and relaxation of supercoiled DNA [8, 9]. Due to its critical function in chromosome condensation and segregation in proliferation and division of cell [8], TOP2A has been widely investigated in multiple diseases including cancer.

In a variety of the malignant tumors, TOP2A protein expression and TOP2A gene status are usually abnormal. However, the relationships between TOP2A and the prognosis of malignant tumor were not consistent. For example, Ito F et al. revealed that the patients with high expression of TOP2A who suffering from endometrial cancer had a poor prognosis in Japanese, which maybe because that TOP2A immunoexpression significantly correlated with advanced stages and tumor aggressiveness [11]. While in another study, Won HS et al. suggested that high expression of TOP2A in breast cancer had no significant predictive value for disease free survival (DFS), which showed limited association between disease free survival (DFS) and overall survival (OS) in Australia, which showed limited association between amplification of TOP2A and the prognosis of breast cancer [17].

Until now, no clear conclusion on the association between TOP2A and the prognosis of malignant tumor has been drawn. In order to explore the relationship between the two, we made a retrospective meta-analysis in this study to elucidate the prognostic role of TOP2A in cancer.

Materials and methods

Identification and eligibility of relevant studies

We conducted a systematically literature search on the electronic databases including PubMed and Web of Science. Different combinations of the following key words were used including “TOP2A/topoisomerase II alpha”, “cancer/malignancy/malignant tumor”, and “survival/prognosis”. In case the data provided in the article were not sufficiently enough, the authors were contacted for specific raw data. When overlapping data were detected, only the latest and largest sample could be adopted for this meta-analysis. July 21th, 2017 was the last search date.

Inclusion and exclusion criteria

Studies included in this meta-analysis must pass the inclusion criteria as follows: studies concerning the relationship between TOP2A and the prognosis of malignant tumor; studies should be published in English; studies should contain sufficient raw data to assess Hazard Ratio (HR) and their 95% confidence interval (CI). The principle for exclusion criteria were reviews or letters; meta-analysis; no relevance; animal experiments for TOP2A; drug sensitivity studies; functional studies of TOP2A; duplicate publications; and studies not about TOP2A.

Data extraction

Two authors (Ling Ren and Jingwei Liu) extracted the data independently from the included studies. From each individual study, the following information was extracted: first author’s name, year of publication, ethnicity and region of the population, the classification of cancer, numbers of patient, the detection methods of TOP2A, Hazard Ratio (HR) and their 95% confidence interval (CI). After discussion, the conflict was resolved, and all the extracted information has reached a consensus.
Statistical analysis

The statistical analysis of this study was carried out by Stata software (Version 11.0; Stata Corp, College Station, TX). Hazard Ratio (HR) and their 95% confidence interval (CI) were applied to assess the strength of the association between TOP2A and the prognosis of malignant tumor. P value <0.05 was considered as statistical significance. Heterogeneity was valued by using Q statistic (P < 0.05 means significant heterogeneity between studies) and I-squared (I²) value [18]. When the heterogeneity between the studies showed no significance, the pooled ORs were calculated using the fixed-effects model of the Mantel-Haenszel method [19]. On the contrary, a random-effects model using DerSimonian and Laird method [20] was used. Subgroup analyses were performed to investigate the effects of ethnicity. In addition, we evaluated publication bias quantitatively by Begg’s test [21] and Egger’s test [22], respectively. P value <0.05 for Begg’s and Egger’s tests represents significant publication bias.

Results

Study characteristics

Using different combinations of key words, a total of 237 literatures were initially selected from the PubMed and Web of Science after duplicates removed. Through reading the titles and abstracts of these potential useful literatures, 165 literatures were excluded mainly by the reason of irrelevant literatures, reviews or meta-analysis, animal experiments, functional research, drug sensitivity study, not raw data. Then, the left 72 full-text literatures were further valued for eligibility. Finally, we adopted 25 full-text literatures [8, 11-13, 16, 17, 23-41] with eligibility in our meta-analysis. The details of the flow chart of literatures selection was shown in Figure 1.

We summarized the major characteristics of these eligible literatures in this meta-analysis in Table 1. All the included literatures were published in English. Twelve articles [11-13, 23-29, 32, 38] investigated the association between TOP2A expression and the prognosis of malignant tumor for HR; thirteen articles [8, 13, 16, 17, 28, 30, 31, 33-37, 40] researched the relationship between the amplification of TOP2A gene and the cancer prognosis for HR; four articles [34, 39-41] studied the association between the alteration of TOP2A gene and the prognosis of cancer for HR. The types of cancers covered breast cancer, endometrial cancer, adrenocortical cancer, of which breast cancer accounts for the vast majority. The detection methods of TOP2A contained IHC, qPCR, and FISH/CISH/SISH. The regions of the population were divided into Asia, Europe, America and Australia. In the subgroup analysis, data concerning different regions were separated as individual studies.

Figure 1. The flowchart of literature inclusion and exclusion
**Table 1. Characteristics of eligible studies in this meta-analysis.**

| Author                | Year | Cancer type            | Region          | Ethnicity | Number | U/M | Expression | Method |
|-----------------------|------|------------------------|-----------------|-----------|--------|-----|------------|--------|
| High expression and OS|      |                        |                 |           |        |     |            |        |
| Chen, J. R.           | 2017 | Breast cancer          | Asia            | Taiwan    | 309    | U   | Protein    | IHC    |
| Wachter, D. L.        | 2013 | Breast cancer          | Europe          | German    | 100    | U   | Protein    | IHC    |
| Itw, F.               | 2016 | Endometrial cancer     | Asia            | Japanese  | 56     | M   | Protein    | IHC    |
| Ip, J. C.             | 2015 | Adrenocortical carcinoma | Australia   | Australian | 61   | M   | Protein    | IHC    |
| Fountzilas, G.        | 2012 | HER-2+ breast cancer   | Australia       | Australian | 57    | U   | Protein    | IHC    |
| Fountzilas, G.        | 2012 | HER-2 breast cancer    | Australia       | Australian | 37    | U   | Protein    | IHC    |
| Nikolentni, A.        | 2012 | Breast cancer          | Europe          | Hungarian | 106   | U   | Protein    | IHC    |
| Fountzilas, G.        | 2012 | Breast cancer          | Australia       | Australian | 314   | M   | RNA        | qPCR   |
| Fountzilas, G.        | 2012 | Breast cancer          | Australia       | Australian | 273   | U   | Protein    | IHC    |
| O’Malley, F. P.       | 2011 | Breast cancer          | North America   | Canadian   | 477   | U   | Protein    | IHC    |
| Roca, E.              | 2017 | Adrenocortical cancer  | Europe          | European   | 98    | M   | Protein    | IHC    |
| Zacze, A. J.          | 2012 | Breast cancer          | Europe          | Polish     | 322   | M   | DNA        | qPCR   |
| High expression and DFS|    |                        |                 |           |        |     |            |        |
| Milde-Langosch, K.    | 2013 | Triple-negative breast cancer | Europe | German | 95   | U   | RNA       | Microarray |
| Milde-Langosch, K.    | 2013 | HER2-positive breast cancer | Europe | German | 69   | U   | RNA       | Microarray |
| Roca, E.              | 2017 | Adrenocortical cancer  | Europe          | European   | 98   | M   | Protein    | IHC    |
| Fountzilas, G.        | 2012 | Breast cancer          | Australia       | Australian | 273   | U   | Protein    | IHC    |
| Ip, J. C.             | 2015 | Adrenocortical carcinoma | Australia | Australian | 77   | U   | Protein    | IHC    |
| Won, H. S.            | 2014 | Breast cancer          | Asia            | Korean     | 70    | M   | Protein    | IHC    |
| Wachter, D. L.        | 2013 | Breast cancer          | Europe          | German     | 100   | U   | Protein    | IHC    |
| Fountzilas, G.        | 2012 | Breast cancer          | Australia       | Australian | 314   | U   | RNA        | qPCR   |
| Zacze, A. J.          | 2012 | Breast cancer          | Europe          | Polish     | 322   | M   | DNA        | qPCR   |
| Amplification and OS  |      |                        |                 |           |        |     |            |        |
| Gogas, H.             | 2016 | Breast cancer          | Europe          | Greece     | 119   | M   | DNA       | FISH |
| Fasching, P. A.       | 2014 | Breast cancer          | Europe          | German     | 628   | M   | DNA       | FISH |
| Fountzilas, G.        | 2012 | HER2+ breast cancer    | Australia       | Australian | 50    | U   | DNA       | FISH |
| Kim, A.               | 2012 | Breast cancer          | Asia            | Korean     | 567   | U   | DNA       | SISH |
| Tubbs, R.             | 2009 | Breast cancer          | America         | American   | 1626  | M   | DNA       | FISH |
| Nielsen, K. V.        | 2008 | Breast cancer          | Europe          | Danish     | 773   | M   | DNA       | FISH |
| Arriola, E.           | 2007 | Breast cancer          | Europe          | British    | 232   | M   | DNA       | CSISH |
| Engstrom, M. J.       | 2014 | Breast cancer          | Europe          | Norwegian  | 670   | U   | DNA       | FISH |
| Fountzilas, G.        | 2012 | Breast cancer          | Australia       | Australian | 266   | U   | DNA       | CSISH |
| Fountzilas, G.        | 2013 | Breast cancer          | Australia       | Australian | 979   | M   | DNA       | FISH |
| Bartlett, J. M.       | 2015 | Breast cancer          | Europe          | British    | 3098  | U   | DNA       | FISH |
| Bartlett, J. M.       | 2010 | Breast cancer          | Europe          | British    | 1762  | U   | DNA       | FISH |
| Lamy, P. J.           | 2011 | HER2-amplified breast cancer | Europe | French | 86   | U   | DNA       | qPCR |
| Fountzilas, G.        | 2013 | Breast cancer          | Australia       | Australian | 979   | M   | DNA       | FISH |
| Kim, A.               | 2012 | Breast cancer          | Asia            | Korean     | 567   | U   | DNA       | SISH |
| Tubbs, R.             | 2009 | Breast cancer          | America         | American   | 1626  | M   | DNA       | FISH |
| Arriola, E.           | 2007 | Breast cancer          | Europe          | British    | 232   | M   | DNA       | CSISH |
| Fountzilas, G.        | 2012 | Breast cancer          | Australia       | Australian | 266   | M   | DNA       | CSISH |
| Amplification and RFS |      |                        |                 |           |        |     |            |        |
| Bartlett, J. M.       | 2010 | Breast cancer          | Europe          | British    | 1762  | U   | DNA       | FISH |
| Lamy, P. J.           | 2011 | HER2-amplified breast cancer | Europe | French | 86   | U   | DNA       | qPCR |
| Nielsen, K. V.        | 2008 | Breast cancer          | Europe          | Danish     | 773   | M   | DNA       | FISH |
| Bartlett, J. M.       | 2015 | Breast cancer          | Europe          | British    | 3098  | U   | DNA       | FISH |
| Alteration and OS     |      |                        |                 |           |        |     |            |        |
| Pritchard, K. I.      | 2012 | Breast cancer          | North America   | Canadian   | 430   | M   | DNA       | FISH |
| Bartlett, J. M.       | 2010 | Breast cancer          | Europe          | British    | 1762  | M   | DNA       | FISH |
| O’Malley, F. P.       | 2009 | Breast cancer          | North America   | Canadian   | 438   | M   | DNA       | FISH |
| Bartlett, J. M.       | 2015 | Breast cancer          | Europe          | British    | 3098  | U   | DNA       | FISH |
| Alteration and DFS    |      |                        |                 |           |        |     |            |        |
| Pritchard, K. I.      | 2012 | Breast cancer          | North America   | Canadian   | 430   | M   | DNA       | FISH |
| Bartlett, J. M.       | 2010 | Breast cancer          | Europe          | British    | 1762  | M   | DNA       | FISH |
| O’Malley, F. P.       | 2009 | Breast cancer          | North America   | Canadian   | 438   | M   | DNA       | FISH |
| Bartlett, J. M.       | 2015 | Breast cancer          | Europe          | British    | 3098  | U   | DNA       | FISH |

IHC: Immunohistochemistry; FISH: Fluorescence in situ hybridization; CISH: Chromogenic in situ hybridization; SISH: Silver-enhanced in situ hybridization; qPCR: Quantitative real time polymerase chain reaction

**Association between TOP2A expression and cancer prognosis**

Individuals with high expression of TOP2A was observed to be associated with shorter disease free survival (DFS) of the cancer prognosis compared with low expression of TOP2A (HR = 1.36, 95% CI = 1.18-1.57, P < 0.001). No significant association was found between TOP2A expression and overall survival (OS) (HR = 1.25, 95% CI = 0.91-1.71, P = 0.163). Subgroup analysis based on regions suggested that high expression of TOP2A was consistently

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related with worse OS and DFS in Europe (OS: HR = 1.38, 95% CI= 1.01-1.73, P=0.005; DFS: HR= 1.28, 95% CI= 1.07-1.52, P=0.007). As for Australia, high expression indicated unfavorable DFS (HR= 1.80, 95% CI = 1.07-3.04, P = 0.028), while there was no significant association between TOP2A expression and OS (HR= 1.48, 95% CI= 0.79-2.78, P= 0.218).

**Association between amplification of TOP2A gene and cancer prognosis**

No significant association was found between amplification of TOP2A gene OS, DFS or relapse free survival (RFS) compared with non-amplification of TOP2A (OS: HR= 0.96, 95% CI= 0.75-1.22, P= 0.735; DFS: HR= 0.93, 95%CI= 0.70-1.23, P= 0.621; RFS: HR = 0.97, 95%CI = 0.71-1.34, P= 0.867). Due to the small sample numbers, we did not conduct subgroup investigations in these two groups.

**Association between alteration of TOP2A gene and cancer prognosis**

Patients with alteration (amplification or deletion) of TOP2A gene demonstrated shorter survival according to OS and RFS compared with those with normal TOP2A status (OS: HR= 1.37, 95%CI= 1.22-1.55, P<0.001; RFS: HR= 1.26, 95%CI= 1.12-1.41, P<0.001). As the number of samples is small, no subgroup analysis was performed by different regions.

### Table 2. Meta-analysis results of the association between expression of TOP2A, amplification or alteration of TOP2A and cancer prognosis for pooled HR.

| Comparison                  | Categories | Group/subgroup | Data set number | HR(95%CI)  | P value | Model | P value | P (%) |
|-----------------------------|------------|----------------|-----------------|------------|---------|-------|---------|-------|
| Expression (High vs. Low)   | OS         | Overall        | 12              | 1.25(0.91-1.71) | 0.163   | F     | <0.001 | 71.20% |
|                             |            | Europe         | 4               | 1.38(1.10-1.73) | 0.005   | F     | 0.068  | 57.90% |
|                             |            | Australia      | 5               | 1.46(0.79-2.78) | 0.218   | F     | <0.001 | 81.50% |
|                             | DFS        | Overall        | 11              | 1.36(1.18-1.57) | 0.001   | F     | 0.137  | 32.80% |
|                             |            | Europe         | 6               | 1.28(1.07-1.52) | 0.007   | F     | 0.257  | 23.60% |
|                             |            | Australia      | 3               | 1.80(1.07-3.04) | 0.028   | F     | 0.044  | 67.90% |
| Amplification (Amp vs. non-Amp) | OS         | Overall        | 13              | 0.96(0.75-1.22) | 0.735   | F     | 0.003  | 59.40% |
|                             |            | Europe         | 8               | 1.07(0.80-1.45) | 0.644   | F     | 0.007  | 64.10% |
|                             |            | Australia      | 3               | 0.66(0.46-0.96) | 0.029   | F     | 0.115  | 53.80% |
|                             | DFS        | Overall        | 5               | 0.93(0.70-1.23) | 0.621   | F     | 0.072  | 53.60% |
|                             |            | RFS            | 4               | 0.97(0.71-1.34) | 0.867   | R     | 0.036  | 64.80% |
| Alteration (Altered vs. Normal) | OS         | Overall        | 4               | 1.37(1.22-1.55) | <0.001  | F     | 0.258  | 28.90% |
|                             | RFS        | Overall        | 4               | 1.26(1.12-1.41) | <0.001  | F     | 0.191  | 36.90% |

R: random effect model; F: fixed effect model; OS: overall survival; DFS: disease free survival; RFS: relapse free survival

### Table 3. Publication bias.

| Comparison                  | Group/subgroup | Categories | Begg's test | Egger's test |
|-----------------------------|----------------|------------|-------------|--------------|
| Expression (High vs. Low)   | Overall        | OS         | 0.41        | 0.681        |
|                             |                | DFS        | 0.39        | 0.697        |
| Amplification (Amp vs. non-Amp) | Overall        | OS         | -0.37       | 0.714        |
|                             |                | DFS        | -0.49       | 0.624        |
| Alteration (Altered vs. Normal) | Overall        | OS         | -1.36       | 0.174        |
|                             |                | RFS        | -1.36       | 0.174        |
Figure 2. A: Forest plot for the association between TOP2A expression and cancer prognosis by OS; B: Forest plot for the association between TOP2A expression and cancer prognosis by DFS
Figure 3. A: Forest plot for the association between amplification of TOP2A and cancer prognosis by OS; B: Forest plot for the association between amplification of TOP2A and cancer prognosis by DFS.
Figure 4. A: Forest plot for the association between alteration of TOP2A and cancer prognosis by OS; B: Forest plot for the association between alteration of TOP2A and cancer prognosis by RFS

Discussion

Although TOP2A has been researched extensively in various malignant tumors, the relationship between TOP2A and prognosis of cancer were inconclusive according previous individual literatures. Studies mainly focused on the influence of either TOP2A expression or copy number variation on clinical outcome of cancer. In this study, we performed a meta-analysis to research the association between the two above with cancer prognosis separately. As far as we know, this is the first
comprehensive meta-analysis exploring the role of TOP2A in tumor prognosis. After analyzing the data extracted from 25 full-text case-control publications, we unraveled that both high TOP2A expression and alteration of TOP2A gene may indicated worse prognosis of cancer.

Uncontrollable high proliferation rates proved to be the main characters of malignant tumor [1]. In proliferating cells, DNA is the key regulator as genetic material. During replication, transcription, recombination and repair of DNA, DNA helix would inevitably occur unwinding or rewinding, bringing out DNA entanglement [42]. DNA topoisomerases are a family of nature's tools which can resolve these problems via the introduction of temporary single or double strand breaks in DNA [5]. As one of the isoenzymes of DNA topoisomerases, TOP2A is obviously up-regulated during these processes [6]. Therefore, TOP2A could perform a predominant role in proliferating cells and may probably be implicated in carcinogenesis.

In this meta-analysis, we observed that high TOP2A expression predicted worse prognosis of cancer. The relationship of high TOP2A expression with shorter DFS in both Europe and Australia remained significant, which indicated that ethnicity had little influence on the predictive role of TOP2A. A number of mechanism studies have explored the effect of TOP2A on cancer development [23, 43-46], which might, at least in part, explain the findings of our investigation. It was found in prostate cancer cells that knockdown of TOP2A decreased proliferation and tumorigenicity [43]. Meanwhile, TOP2A was upregulated in recurrence/metastasis prostate cancer [43]. Therefore, the close relationship between TOP2A up-regulation and increased proliferation of cancer cells account for its effect on poorer prognosis. These findings also provided significant implications for prostate cancer therapy that treatments to kill TOP2A positive cells may provide a better method to eradicate primary prostate cancer [43]. As an oncogene, HER2 resides on the long arm of chromosome 17, which is the same location with TOP2A [45, 46]. Accordingly, TOP2A amplification always came with HER2 amplification because amplification of one gene locus could simultaneously overexpress both of these genes [45]. As most well-known cancer suppressor genes, p53 and pRB are negative regulators of TOP2A [23, 44, 45]. The commonly inactivated and deleted of these two protective genes in cancer partly lead to the overexpression of TOP2A [45]. The phenomenon of oncogene up-regulation and cancer suppressor gene down-regulation upon high TOP2A expression in cancer would probably contribute to the unfavourable survival. TOP2A also determine the outcome of tumor chemotherapy. Colorectal cell-line SW620 overexpressing TOP2A demonstrated significant resistance to chemotherapeutic treatment with irinotecan and etoposide, which resulted from suppression of apoptosis in TOP2A over-expressed cells [47]. Resistant to chemotherapeutic regimen make it reasonable why patients with TOP2A overexpression suffered shorter survival. Our results in this meta-analysis concerning the correlation between high expression of TOP2A and poorer survival outcomes enhance its role in cancer development. As for clinical applications, TOP2A might serve as indicator for poor prognosis. In addition, targeting TOP2A high expression cells might be a novel treatment for malignant tumors.

Copy number variation (CNV), caused by the genome rearrangement, refers to the length of 1 kb or more large fragments of the genome copy number amplification or deletion [48]. Alteration of TOP2A copy number variation (amplification and deletion) has been found to be significantly increased in high histologic grade cancers whereas no TOP2A copy number variation was detected in well-differentiated tumors [49]. According to the results of our meta-analysis, alternation of TOP2A gene copy number variations (amplification and deletion) significantly correlated with shorter survival from aspects of both OS and RFS. It seems that as a key regulator of genetic process of cells, neither amplification nor deletion of TOP2A gene benefits the clinical outcome of cancer patients. Results of some investigations could explain these findings: both amplification and deletion of TOP2A gene were associated with polysomy of chromosome 17 [50]. Chromosome 17 polysomy was one of the frequent major abnormality events and correlated with aggressive biological behavior of breast cancer [51, 52]. In addition, Knoop et al. reported that significant relationship of TOP2A-amplified/TOP2A-deleted breast cancers with tumor size, nodal involvement and ER positivity [53]. Furthermore, TOP2A gene is located in close proximity to oncogene HER-2 locus on chromosome 17. Some investigators suggested that TOP2A amplification and deletion may not be two different ends of a continuum, but rather be regarded as an abnormal status to be distinguished from the normal status of HER-2 protein [54]. As a result, the examination of the abnormal status of TOP2A gene might serve as a helpful biomarker which could indicate severity of patients suffering cancer in the future.

In this study, we revealed no relationship between amplification of TOP2A gene and prognosis of cancer, except for the subgroup of Australia.
population. The findings that TOP2A amplification predicted longer overall survival in Australia might due to the different background of ethnicity. One study performed in Taiwanese invasive female breast cancers by tissue microarrays suggested no prognostic value of TOP2A amplification [32]. Besides, studies have indicated potential of TOP2A amplification as a useful clinical biomarker of sensitivity to adjuvant anthracycline-based chemotherapy in patients with breast cancers pertaining to the HER2 positive subgroup in British [16]. Patients with TOP2A amplifications showed a 51% reduction in the risk of death in breast cancer if allocated to CEF (cyclophosphamide, epirubicin, and fluorouracil) compared with TOP2A normal patients [8]. Study of TOP2A gene amplification in malignant cancer patients may affect the decision of taking adjuvant chemotherapy and thus protect patients from therapy-induced complications. Considering the limited sample size, the correlation between TOP2A gene amplification with survival time of cancer still need further investigations to confirm due to the limited sample size in specific subgroup.

We should acknowledge some limitations in this meta-analysis. First, only literatures published in English were included. Second, the sample capacity in the pooled analysis and some subgroup analyses was relatively small. Therefore, the results still need large-scale studies to confirm later. Third, other important personal data as age, sex, and family history were not applicable for each study, so we could not get results with adjustments by other co-variates. Fourth, the combination of different sequencing methods and different types of cancers may lead to heterogeneity of the population and reduce the strength of the study.

Conclusion

To be concluded, our meta-analysis suggested that high TOP2A expression predicted worse prognosis of cancer. Alteration (amplification or deletion) of TOP2A gene also showed significant relation with shorter survival for cancer patients. Therefore, TOP2A might serve as novel prognostic indicator for the prognosis of malignant tumor. Further well-designed and large-scale investigations concerning different regions are still necessary to prove the conclusion of our meta-analysis.

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Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

Competing Interests

The authors have declared that no competing interest exists.

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