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Research Paper

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, archaebacteria 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 application value of TOP2A as a prognostic marker [12]. However, another article pointed out that overexpression of TOP2A in HER2-positive and HER2-negative breast tumors had an obviously opposite prognostic impact in Australia, which indicated possible relationship between TOP2A and HER2 [13].

In addition, the role of *TOP2A* copy number variation in the development and prognosis of tumors was still unclear. In invasive carcinoma with adjacent ductal carcinoma in situ (DCIS-AIC), *TOP2A* showed a lower frequency of copy number increase in males compared to females, which indicate probable differences in breast carcinogenesis between the different sexes[14]. Kaya I et al. found no significant association between *TOP2A* deletion and abnormal cytologic findings in cervical cell lesions [15]. As for the clinical implications, the amplification of *TOP2A* in the patients who underwent *HER2* amplified breast tumors predicted a better overall survival (OS) and disease free survival (DFS) in British, offering a possibility that amplification of *TOP2A* might be a useful marker to predict cancer prognosis [16]. But another investigation found that *TOP2A* amplification demonstrated no association with 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 (I^2) 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.

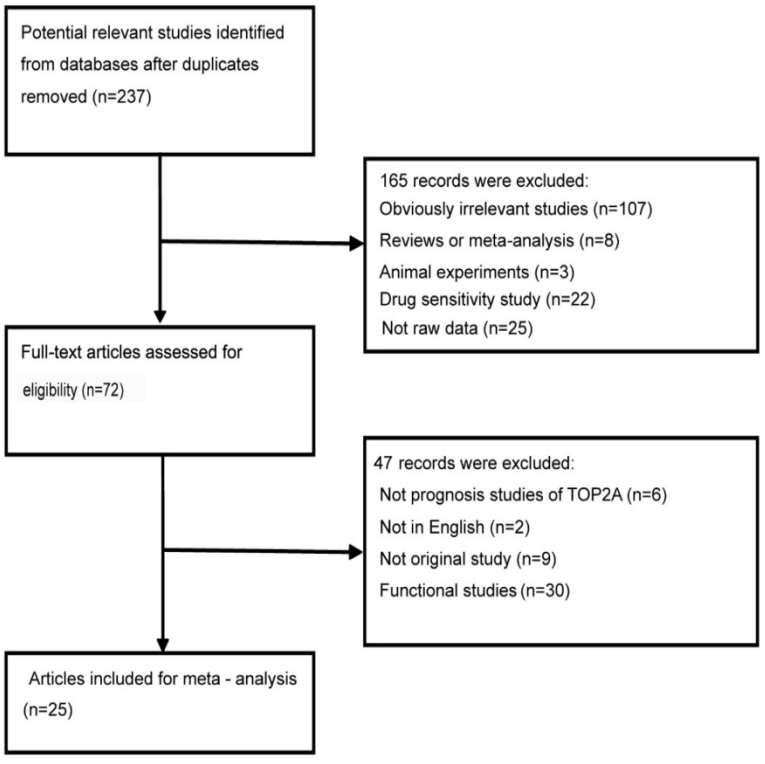

Figure 1. The flowchart of literature inclusion and exclusion

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
Ito, 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
Nikolenyi, 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
Zaczek, 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
Milde-Langosch, K.	2013	Luminal breast cancer	Europe	German	397	M	RNA	Microarray
Roca, E.	2017	Adrenocortical cancer	Europe	European	98	M	Protein	IHC
Fountzilas, G.	2012	Breast cancer	Australia	Australian	273	U	Protein	IHC
Ito, F.	2016	Endometrial cancer	Asia	Japanese	56	M	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
Zaczek, 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	HER-2+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	CISH
Engstrom, M. J.	2014	Breast cancer	Europe	Norwegian	670	U	DNA	FISH
Fountzilas, G.	2012	Breast cancer	Australia	Australian	266	U	DNA	CISH
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
Amplification and DFS								
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	CISH
Fountzilas, G.	2012	Breast cancer	Australia	Australian	266	M	DNA	CISH
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 RFS								
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

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). When considering the effect of regions, *TOP2A* amplification predicted longer overall survival (HR= 0.66, 95%CI= 0.46-0.96, P= 0.029) in Australia, while no significant association was observed between *TOP2A* amplification and OS in the subgroup of Europe (HR= 1.07, 95%CI= 0.80-1.45, P= 0.644). Due to the small sample numbers, no subgroup analysis was performed by different regions in the two groups: amplification of *TOP2A* with DFS and RFS.

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, we did not conduct subgroup investigations in these two groups.

Heterogeneity

The heterogeneity results were summarized in Table 2, of which only some comparisons showed significant heterogeneity. This heterogeneity could not be completely eliminated by subgroup analysis. In addition, due to the limited study number, we did not make a meta-regression to explore the source of heterogeneity. For certain relationship such as alteration of *TOP2A* and cancer prognosis based on OS and RFS, no significant heterogeneity was detected (P>0.05). Excluding each study did not significantly alter the overall outcome, indicating that the results of this meta-analysis were robust.

Publication Bias

The Begg's test and Egger's test were adopted to quantitatively assess the publication bias in the literatures. No significant publication bias was observed for meta-analyses between high expression of TOP2A, amplification or alteration of *TOP2A* and the prognosis of malignant tumor. We summarized the results for publication bias test in Table 3.

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	I^2 (%)
Expression (High vs. Low)	OS	Overall	12	1.25(0.91-1.71)	0.163	R	<0.001	71.20%
		Europe	4	**1.38(1.10-1.73)**	**0.005**	F	0.068	57.90%
		Australia	5	1.48(0.79-2.78)	0.218	R	<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**	R	0.044	67.90%
Amplification(Amp vs. non-Amp)	OS	Overall	13	0.96(0.75-1.22)	0.735	R	0.003	59.40%
		Europe	8	1.07(0.80-1.45)	0.644	R	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	Overall	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	0.238	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.

			Begg's test		Egger's test	
Comparison	Group/subgroup	Categories	z value	P value	t value	P value
Expression(High vs. Low)	Overall	OS	0.41	0.681	0.15	0.883
		DFS	0.39	0.697	1.04	0.324
Amplification(Amp vs. non-Amp)	Overall	OS	-0.37	0.714	-0.61	0.556
		DFS	-0.49	0.624	0.10	0.926
		RFS	0.00	1.000	-0.26	0.817
Alteration(Altered vs. Normal)	Overall	OS	-1.36	0.174	-2.72	0.113
		RFS	-1.36	0.174	-1.41	0.293

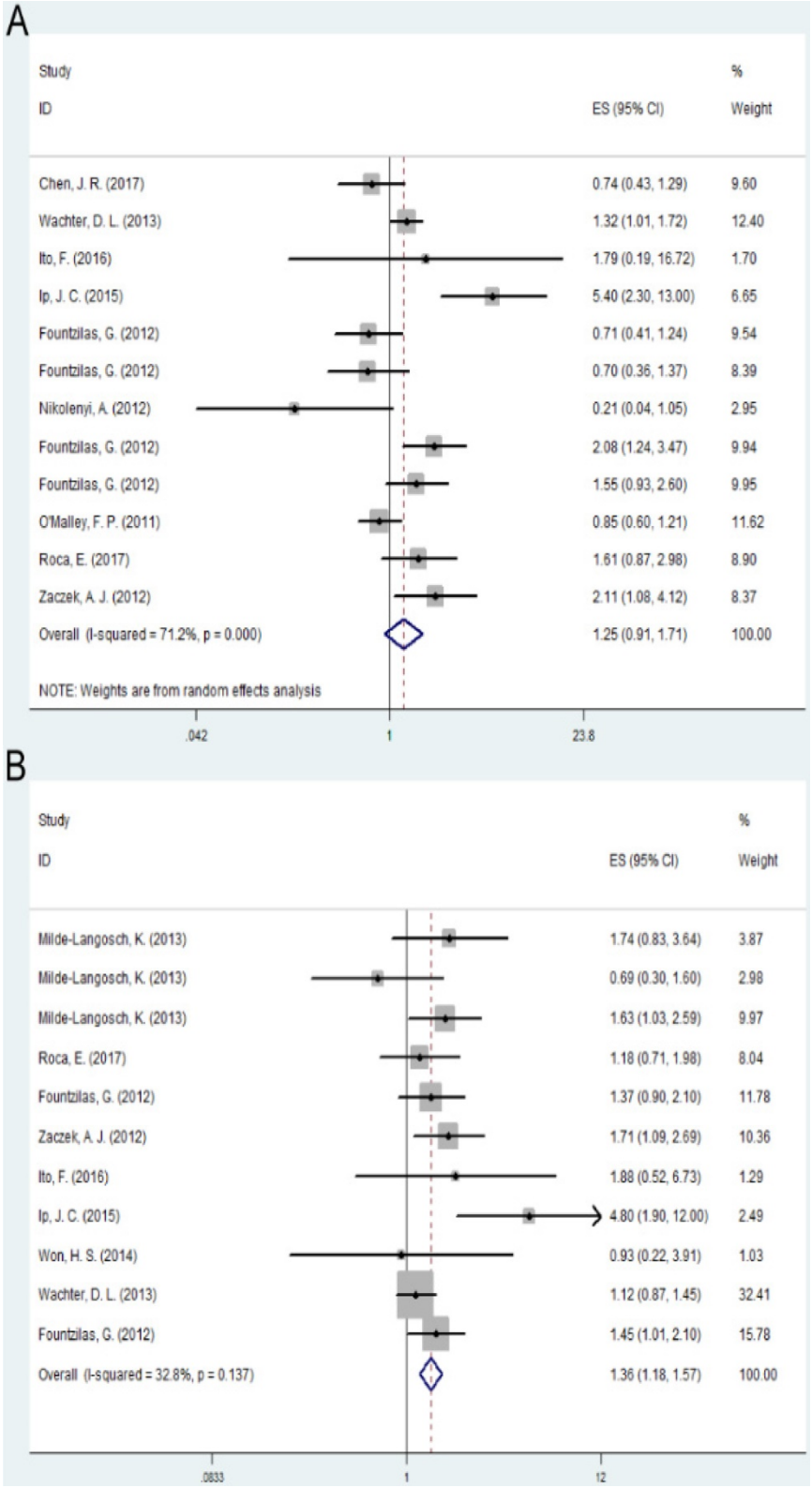

Figure 2. A: Forest plot for the association between TOP2A expression and cancer prognosis by OS; B: Forest plot for the association between TOP2A expression and cancer prognosis by DFS

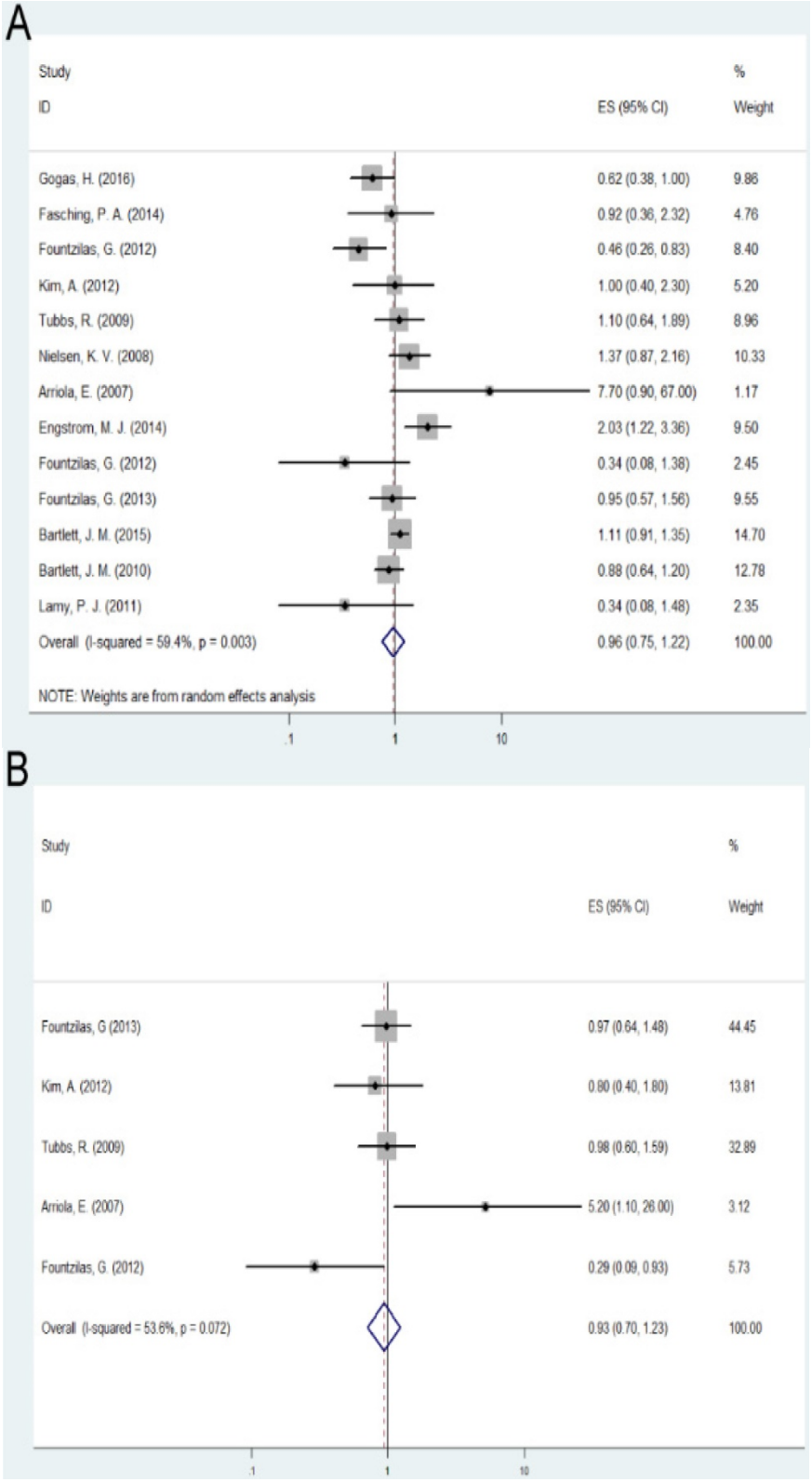

Figure 3. A: Forest plot for the association between amplification of *TOP2A* and cancer prognosis by OS; B: Forest plot for the association between amplification of *TOP2A* and cancer prognosis by DFS

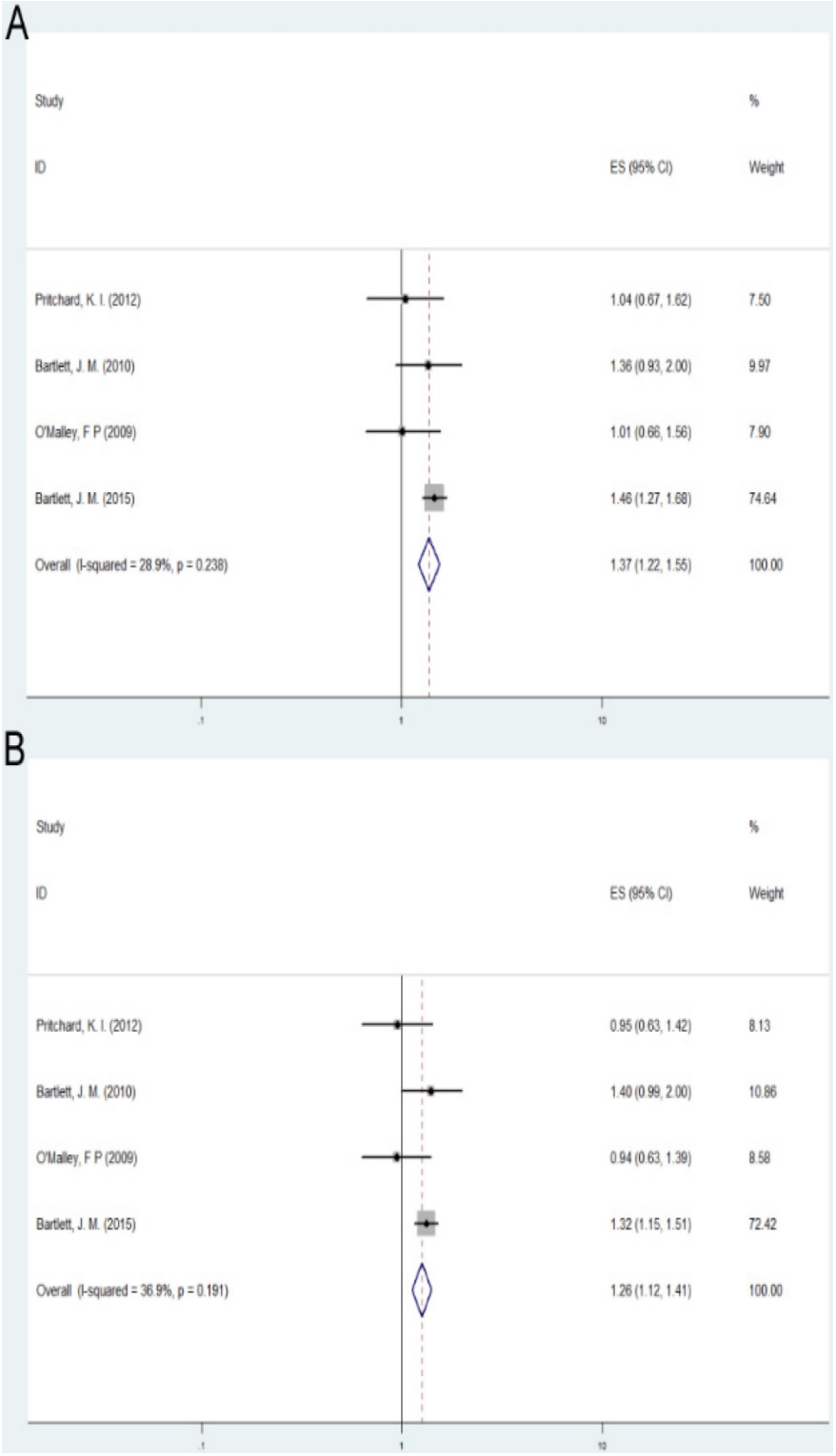

Figure 4. A: Forest plot for the association between alteration of *TOP2A* and cancer prognosis by OS; B: Forest plot for the association between alteration of *TOP2A* and cancer prognosis by RFS

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]. Alternation 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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