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Prognostic and Clinicopathological Value of SIRT1 Expression in Female Reproductive System Cancer

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Abstract: Objective: Numerous epidemiological studies have reported the association between silent mating type information regulation 2 homolog-1 (SIRT1) and female reproductive system cancer, but the data of different reports remains controversial. To accurately evaluate the significance of SIRT1 expression in reproductive system cancer, a meta-analysis based on published studies was conducted. **Methods**: Relevant articles before August 2017 on SIRT1 and reproductive system cancer were searched via PubMed, Embase, Cochrane Central and Chinese National Knowledge Infrastructure databases(NCBI). The studies were chosen for the meta-analysis based on requisite criteria. The overall survival (OS) and clinical features including FIGO stage , lymph node metastasis (LNM) and tumor grade were analyzed using RevMan 5.3 software. Odds ratios (OR) , hazard ratios (HR) and their 95% corresponding confidence intervals (CI) were pooled to estimate the effect of specific associations. **Results**: A total of 14 eligible studies containing 1002 patients were enrolled, in which 47.9% of the patients overexpressed SIRT1. The results showed that SIRT1 overexpression significantly correlated with the risk of reproductive cancers (OR=3.92, 95% CI: 3.06–5.02, P<0.00001), histological grade (OR=2.47, 95% CI=1.19-5.13, p=0.02), LNM (OR=3.25, 95% CI=1.85-5.70, P<0.0001), but no statistical significance was related to FIGO stage (OR=1.84, 95% CI=1.00-3037, P=0.05) and overall survival (HR=1.32, 95% CI=1.00-1.75, P=0.05) of female reproductive system cancer. **Conclusions**: The overall data of the shown meta-analysis suggested that the expression of SIRT1 is correlated with cancer risk, lymph node metastasis and histological grade. However, the over-expression of SIRT1 have no statistical significance with FIGO stage and overall survival.

Keywords: SIRT1, Reproductive System Cancer, Clinicopathological Characteristics, Prognosis, Meta-Analysis

Introduction

Female reproductive system cancers are among the most threat to cancer-related death, which includes cervical cancer, ovarian cancer, and endometrial cancer. Actually Cervical cancer is the third most common diagnosed malignance and the fourth leading cause of cancer-related death in females worldwide [1], Ovarian cancer is the leading cause of mortality from gynecological malignancy [2], Endometrial cancer is the fifth most normally cancer among female worldwide which accounted for 4.8% of all female cancer cases [3]. Numerous of cell signaling pathways have been explored and studied, accumulating evidence has presented that epigenetic regulation of gene expression contributes highly to reproductive system malignancy [4]. Sirtuins, a highly conserved protein

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family, has been shown to be a significant protease partaking in the initiation and the development of cancer[5].

Silent mating type information regulation 2 homolog-1 (SIRT1), a member of the sirtuin family, is a nicotinamide adenine nucleotide-dependent histone deacetylase[6]. It is reported that SIRT1 involves in a variety of physiological processes, such as aging, metabolism, DNA repair and gene silencing[7-9]. Recent studies suggested that aberrant expression of SIRT1 was found and represent heterogeneity in diverse cancers. The expression of Sirt1 is increased in hepatocellular carcinoma[10-11], lung cancer[12], pancreatic cancer[13], however it is reduced in gastric cancer[14], breast cancer[15]. For this reason, it remains ambiguous whether the up-regulated expression of sirt1 indicates a good prognosis or not. Meanwhile, these studies also revealed that sirt1 expression is linked with many clinicopathological characteristics[10-15],some studies revealed that sirt1 is an independent risk factor in the development of cancer, while others showed no correlation of SIRT1 expression with cinicopathological features.

In this study, we conducted a meta-analysis of published studies to estimate the prognostic and clinicopathological value of SIRT1 in patients with reproductive cancer. The clinical significance of the findings are also discussed.

Materials and Methods

Search strategy and study selection

To get access to potentially eligible studies, we conducted an thorough electronic search for relevant studies using PubMed, Embase, Cochrane Central and Chinese National Knowledge Infrastructure databases(CNKI) (up to August, 2017) with no restriction of origin or language, using various combinations of the following terms: “SIRT1”or“silent mating type information regulation 2 homolog-1”or “sirtuin 1”(all fields) and cancer or tumor or malignancy or neoplasm or carcinoma (all fields), and reproductive system or genital system(all fields), and“prognosis” or “survival” or “clinical outcome”(all fields). The reference lists of relevant articles were searched manually as well.

Publications were considered eligible in our quantitative meta-analysis when they met all of the following criteria: (1) The diagnosis of reproductive cancer was histologically and pathologically confirmed; (2) SIRT1 expression was determined by immunohistochemistry(IHC) in the tissues of reproductive system cancers; (3) Sufficient information of the correlation of SIRT1 with clinicopathological features or overall survival time was provided to estimate odds ratio (OR) and hazard ratio (HR); (4) Being written as full papers; Publications were excluded based on the following criteria: (1) The studies have no relevant with reproductive system cancers or SIRT1; (2) Studies lack of usable statistical data for further analysis; (3) duplicate or overlapping publications; (4) reviews, letters or case reports.

Data extraction and quality assessment

The including studies were reviewed and collected according to the selection criteria by two researchers(zhangshuai and sunzhe)separately. Any disagreement between the two reviewers was resolved by discussion or consult to the third-party. For all eligible studies, the following data was extracted: the first author, year of publication, country of origin, cancer or histological type, number of SIRT1 positive or negative participants(cancer patients’ tissue and comparison tissue), detection method, clinicopathological parameters［including tumor size, lymph node metastasis (LNM), TNM stage, histological grade］, follow-up times, type of survival. Survival data (HR with 95% CI) were extracted from tables or articles of eligible studies. If the articles had Kaplan-Meier curves, Engauge Digitizer V4.1 (http://digitizer.sourceforge.net/) was used to digitize and collect survival data.

Statistical analysis

Data were extracted from the primary articles and meta-analysis was calculated with the use of RevMan5.3 software (Cochrane Collaboration, http://community.cochrane.org/tools/review-production-tools/revman-5/revman-5-download). Odds ratios (OR) and their 95% confidence intervals (CI) were used to assess correlations between SIRT1 expression and the clinicopathological features of reproductive system cancer, including histological grade, LNM, TNM stage. Hazard ratios (HR) and their 95% CI were used for analysis of the effects of SIRT1 expression on overall survival.

Heterogeneity among studies was determined by Chi square-based Q test and I^2 statistics. *P* value higher than 0.05 for the Q test and I^2 value less than 50 % were considered to be of no noteworthy heterogeneity, the fixed effects model was adopted ($P > 0.05$, $I^2 < 50\%$); If not, the random effects model was applied. The publication bias was evaluated by funnel plot. All the statistical tests were two-sided, and $P < 0.05$ was considered as statistically significant publication bias.

RESULTS

Description of the eligible studies

184 related papers was identified through the initial database searching. Based on the criteria for inclusion, after carefully reviewing the abstract and full-text of these literatures, finally, 14 eligible studies published from 2009 to 2017 were enrolled in this meta-analysis. A total of 1002 patients from china[20,21,22,2427,28,29], Japan[18,25], Korea[23,26], India [17], Portugal [19] were diagnosed with different cancers, including cervical cancer[16,17], ovarian cancer [18-22], and endometrial cancer[23-28]. All of these 14 included studies was only evaluated by immunohistochemistry (IHC) method. The expression of SIRT1 was observed only in the nucleus，while it can expressed both in cytoplasm and nucleus. The participants in all the literatures were categorized into high SIRT1 expression group and low SIRT1 expression group. The comparison group including adjacent normal tissue, benign non-neoplastic, benign tumors or borderline malignant tumors. Main characteristics of detailed features were summarized in Table 1.

Table 1: Characteristics of the eligible publications in this meta-analysis.

First author & Year	country	cancer type	case	histological grade	FIGO stage	LNM	SIRT1 high expression(+)	Follow-up times	survival SIRT1 expression (H/A)
Terame，2014[16]	Japan	CC	62	NA	NA	NA	32	120	OS NA
Thakur, 2015[17]	India	CC	67	NA	NA	NA	20	NA	NA 19/73
Asaka, 2015[18]	Japan	EC	108	G1+G2 :24/89 G3 :11/19	Ⅰ+Ⅱ:26/87 Ⅲ+Ⅳ:7/21	NA	29	200	OS+DFS 10/84
Bartosch, 2015[19]	Portugal	EC	76	G1+G2 :26/45 G3 :7/13	Ⅰ+Ⅱ: 35/60 Ⅲ+Ⅳ:1/16	NA	47	NA	NA 6/30

Lin, 2012[20]	China	EC	92	G1+G2:33/51 G3 :35/41	Ⅰ+Ⅱ:35/60 Ⅲ+Ⅳ:27/32	P: 19/21 N:35/71	75	60
OS	50/99							
Guo, 2012[21]	China	EC	95	G1+G2:56/76 G3 :16/16	Ⅰ+Ⅱ:59/75 Ⅲ+Ⅳ:20/20	p:9/11 N:39/48	79	NA
NA	7/40							
Wei, 2014[22]	China	EC	99	NA	NA	NA	60	NA
NA	20/75							
Shin, 2016[23]	Korea	OC	45	NA	NA	NA	16	180
OS	NA							
Shuang, 2015[24]	China	OC	63	G1+G2:34/58 G3 :3/5	Ⅰ+Ⅱ:7/13 Ⅲ+Ⅳ:28/50	P:9/16 N:22/47	31	80
OS	NA							
Mvunta, 2015[25]	Japan	OC	68	NA	Ⅰ+Ⅱ:7/47 Ⅲ+Ⅳ:4/21	P:7/12 N:15/56	11	200
OS	NA							
Jang, 2009[26]	Korea	OC	90	G1+G2:32/74 G3 :5/9	Ⅰ+Ⅱ:19/37 Ⅲ+Ⅳ:18/47	NA	41	137
OS	6/86							
Zhao, 2013[27]	China	OC	65	G1+G2:9/10 G3 :36/55	Ⅰ+Ⅱ:6/11 Ⅲ+Ⅳ:40/54	NA	45	62
OS+DFS	2/38							
Zheng, 2017[28]	China	OC	32	G1+G2:6/17 G3 :13/15	Ⅰ+Ⅱ:4/15 Ⅲ+Ⅳ:14/17	P:11/14 N:4/18	15	NA
NA	1/48							
Shi, 2017[29]	China	OC	40	G1+G2:8/30 G3 :8/10	NA	P:4/8 N:12/32	16	NA
NA	41/60							

Abbreviations: CC: cervical cancer, OC: ovarian cancer, EC: endometrial cancer, H: high expression，L: low expression, A:all samples, LNM: lymph node metastasis, NA: not available, P: positive，N: negative, OS: overall survival, DFS：disease-free survival.

Meta-analysis

In this meta-analysis, we estimated the correlation between SIRT1 expression and cancer risk, clinicopathological features, and overall survival time of patients with female reproductive cancers. The results of SIRT1 expression with cancer risk were listed in Figure 1, Over-expression of SIRT1 was associated with female reproductive cancer risk (OR=3.92, 95% CI: 3.06–5.02). Furthermore, subgroup analysis showed a concordant trend. For example, ovarian cancer (OR=3.82, 95% CI: 2.48–5.86), and endometrial cancer(OR=5.11, 95% CI: 3.63–7.19).

As shown in Figure 2, The combined analysis of 8 literatures showed that the expression of SIRT1 have no related to OS of reproductive cancers statistically (HR = 1.32, 95% CI = 1.00 - 1.75, P = 0.05).

We selected 3 clinicopathological features that were reported in more than 6 articles, regardless of subtype to conduct a correlation analysis between SIRT1 expression and clinical parameters. As shown in Figure 3, there was a concordant correlation between SIRT1 expression and the following two clinical parameters: Histological grade (3 vs.1/2, pooled OR=2.47, 95% CI=1.19-5.13, p=0.02), lymph node metastasis (LNM) (Positive vs. Negative, pooled OR=3.25, 95% CI=1.85-5.70, p < 0.0001). However, no statistical sense was found between SIRT1 expression and FIGO stage (III/IV vs. I/II , pooled OR=1.84, 95% CI=1.00-3.37, p=0.05).

Publication bias

We used the funnel plot to identify the publication bias analysis, no obvious publication bias was found in the meta-analysis (Figure 4).

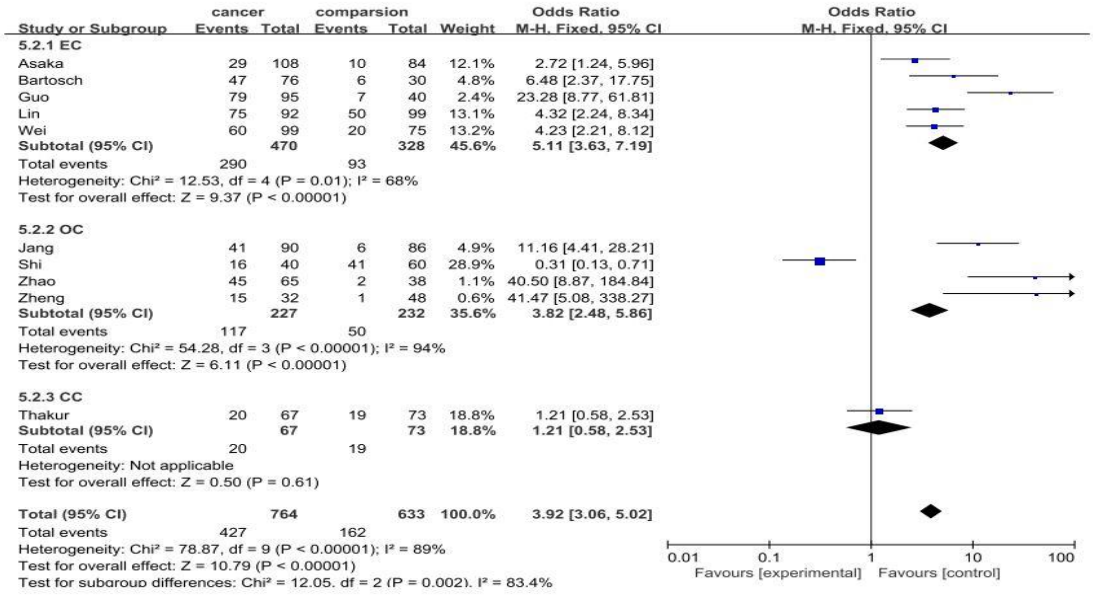

Figure 1. Forest plot of odds ratios (OR) for the association of SIRT1 expression with the risk of female reproductive cancer.

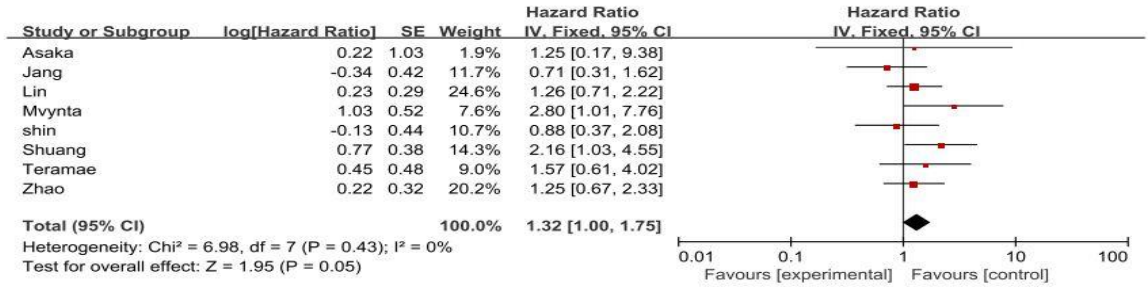

Figure 2. Forest plots of associations between SIRT1 expression with OS in female reproductive cancer.

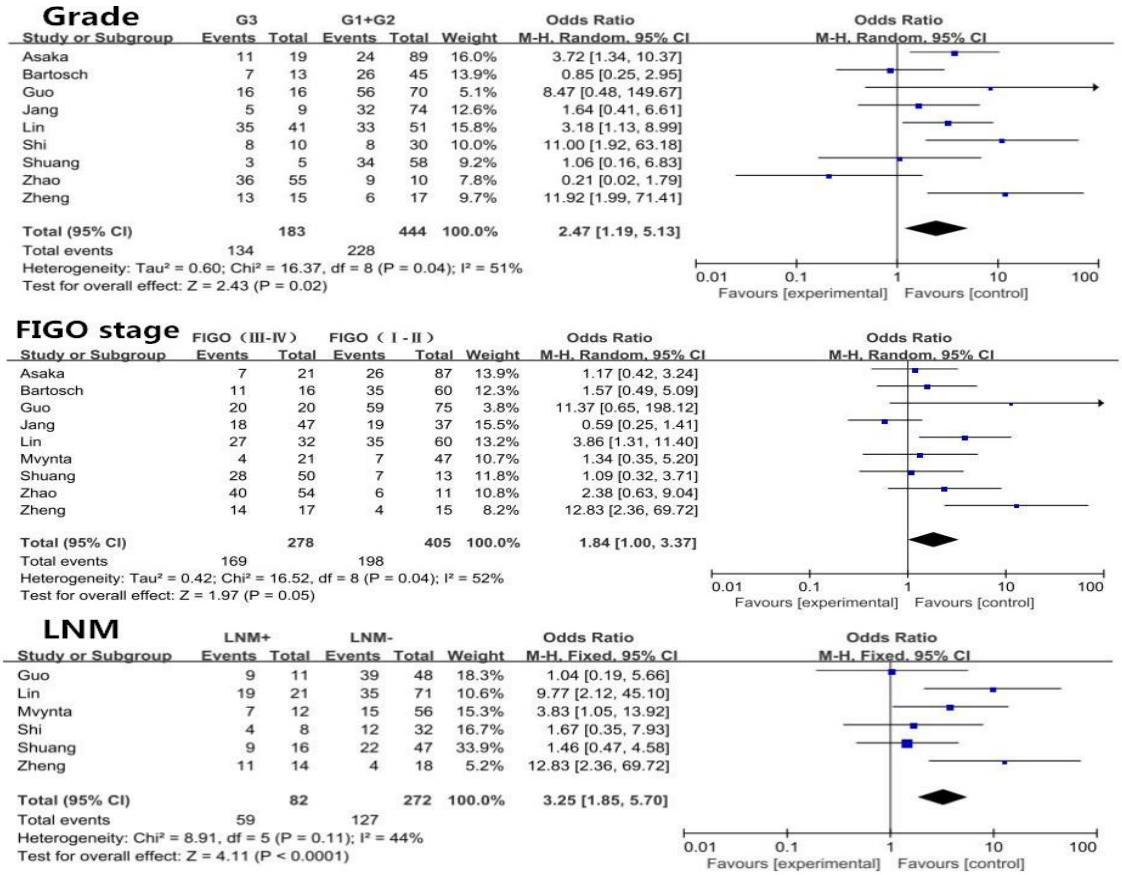

Figure 3. Forest plots of associations between SIRT1 expression with histological grade, FIGO stage and lymph node metastasis (LNM) in female reproductive cancers.

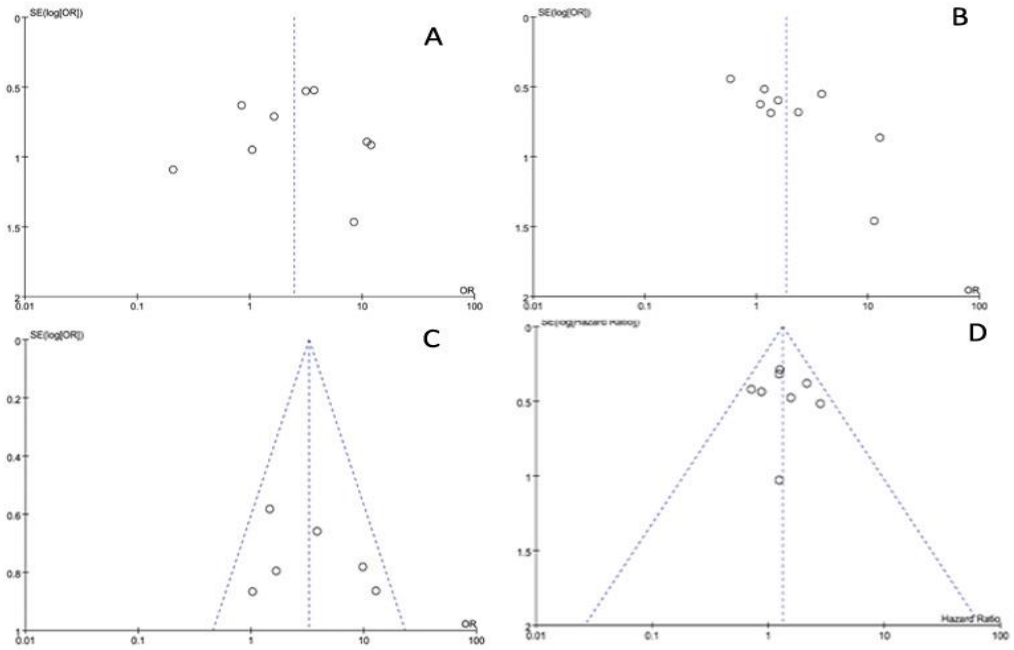

Figure 4. A: The funnel plots of SIRT1 expression with histological grade; B: The funnel plots of SIRT1 expression with FIGO stage; C: The funnel plots of SIRT1 expression with lymph node metastasis (LNM); D: The funnel plots of SIRT1 expression with OS.

Discussion

SIRT1, homologue of the yeast Sir2 protein, is the most well investigated member of the sirtuin family. It acts mainly as lysine deacetylase and has been reported to expressed both in nuclear and cytoplasm[31]. However, the crucial contribution of SIRT1 to carcinogenesis remains a controversy, as some reports suggest that SIRT1 can exert both as a positive or negative regulator of tumorigenesis in different types of cancer. Recently, some studies revealed that the function of SIRT1 hinges on the type of cell or cancer.

To date, the prognostic value of SIRT1 in various cancers has been extensively explored in a group of original researches. Based to the a meta-analysis of SIRT1 overexpression related to prognosis of various solid tumors, wang [30] extracted data from 37 studies and found that elevated SIRT1 expression was significantly associated with shorter OS and RFS of solid malignancies. Although the prognostic value of SIRT1 in some cancer types of reproductive system was also reported in this meta-analysis, the number of included studies was not relatively enough and only 2 eligible studies were included, of which the study merely about OC [23,25]. So, it was difficulty to judge the exact impact of SIRT1 expression on clinical parameters and prognosis related to female reproductive cancer progression and long-term survival. Therefore, we conducted this meta-analysis to study the prognostic and clinicopathological value of SIRT1 on reproductive cancers.

In our meta-analysis,14 studies containing 1002 cancer patients' tissue and 633 comparison tissue (including adjacent normal tissue, benign non-neoplastic , benign tumors or Borderline malignant tumors) were included. Our data showed that SIRT1 over-expression was significantly associated with cancer risk in reproductive cancers. In clinic, FIGO stage , lymph node metastasis (LNM) and tumor grade was the most important clinicopathological parameter for cancer patients, our studies showed that SIRT1 expression was observably associated with the lymph node metastasis (LNM) and tumor grade described above. Unfortunately, the expression of SIRT1 with overall survival, FIGO stage has no statistical significance in reproductive cancer patients.

To the best of our knowledge, our present meta-analysis is the first study to explore the potential relationship between SIRT1 expression and female reproductive cancers. However, some limitations of our meta-analysis should be noted. Firstly, we only included 14 studies (including 2 cervical cancers, 5 ovarian cancers, and 7 endometrial cancers), in which only 8 studies observed the correlation between SIRT1 expression and overall survival time. Besides, the studies distributed mainly about Asian countries, and there was only one literature in western countries. Attributed to the small number of included studies, we failed to conduct a subgroup analysis of OS based on the follow up period. Hence, the association of SIRT1 expression with overall survival time still needs to be studied in a larger number of samples. Secondly, several individual HR were calculated from survival curves or univariate analysis, which may be less reliable than the actual HR directly obtained from published statistics. Finally, owing to most of the cases in the literatures are relatively small, the heterogeneity among the studies remained, despite the usage of a random-effects model and subgroup analyses. The heterogeneity could have generate outcome bias.

In spite of the flaws mentioned above, there is plenty of pragmatic value in our study. Our meta-analysis indicates a positive association between the over-expression of SIRT1 with carcinogenesis, progression of female reproductive cancers. In addition, SIRT1 may be used as a biomarker to predict reproductive system cancer.

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