Survivin -31 G/C polymorphism might contribute to colorectal cancer (CRC) risk: a meta-analysis

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Abstract: Published data has shown inconsistent findings about the association of survivin -31 G/C polymorphism with the risk of colorectal cancer (CRC). This meta-analysis quantitatively assesses the results from published studies to provide a more precise estimate of the association between survivin -31 G/C polymorphism as a possible predictor of the risk of CRC. We conducted a literature search in the PubMed, Web of Science, and Cochrane Library databases. Stata 12 software was used to calculate the pooled odds ratios (ORs) with 95% confidence intervals (CIs) based on the available data from each article. Six studies including 1840 cases with CRC and 1804 controls were included in this study. Survivin -31 G/C polymorphism was associated with a significantly increased risk of CRC (OR = 1.78; 95% CI, 1.53-2.07; $I^2 = 0\%$). In the race subgroup analysis, both Asians (OR = 1.72; 95% CI, 1.44-2.05; $I^2 = 0\%$) and Caucasians (OR = 1.93; 95% CI, 1.46-2.55; $I^2 = 0\%$) with survivin -31 G/C polymorphism had increased CRC risk. In the subgroup analysis according to site of CRC, survivin -31 G/C polymorphism was not associated with colon cancer risk (OR = 2.02; 95% CI, 0.79-5.22; $I^2 = 82\%$). However, this polymorphism was significantly associated with rectum cancer risk (OR = 1.98; 95% CI, 1.42-2.74; $I^2 = 0\%$). In the subgroup analysis by clinical stage, both early stage (I+II) and advanced stage (III+IV) were associated with survivin -31 G/C polymorphism (OR = 1.61; 95% CI, 1.20-2.16; $P = 0\%$ and OR = 2.30; 95% CI, 1.70-3.13; $P = 0\%$, respectively). In the subgroup analysis by smoking status, both smokers and non-smokers with survivin -31 G/C polymorphism showed increased CRC risk (OR = 1.47; 95% CI, 1.01-2.13; $I^2 = 60\%$ and OR = 1.71; 95% CI, 1.28-2.30; $I^2 = 0\%$, respectively). In the subgroup analysis by alcohol status, both drinkers and non-drinkers with survivin -31 G/C polymorphism showed increased CRC risk (OR = 1.58; 95% CI, 1.06-2.37; $I^2 = 8\%$ and OR = 1.61; 95% CI, 1.23-2.11; $I^2 = 0\%$, respectively). In conclusion, this meta-analysis suggested that survivin -31 G/C polymorphism may be associated with the risk of CRC.

Keywords: Colorectal cancer, survivin, meta-analysis, polymorphism

Introduction

Colorectal cancer (CRC) is one of the most common malignancies and represents a significant cause of morbidity and mortality worldwide [1]. Recent progress in diagnosis and therapy has helped to save the lives of many patients at early stages of this malignancy, but the prognosis for patients with advanced disease or metastasis is still poor. Therefore, further investigation into the molecular pathogenesis of CRC and the consequent development of novel targeted therapeutics are needed.

Survivin is a small protein and tumor associated antigen expressed in many cancers. Survivin normally functions as an apoptosis inhibitor, via spindle microtubule and mitotic checkpoint regulation [2]. It is a potential target for immunotherapy since it is highly expressed in many cancers [3], it is linked to worse prognosis in both solid and hematologic tumors, and it is undetectable in almost all normal adult tissues [4].

Published data has shown inconsistent findings about the association of survivin -31 G/C polymorphism with the risk of CRC [5-10]. This meta-analysis quantitatively assesses the results from published studies to provide a more precise estimate of the association between survivin -31 G/C polymorphism as a possible predictor of the risk of CRC.

Methods

Publication search

We conducted a literature search for relevant studies on the relationships between survivin -31 G/C polymorphism and CRC risk in the PubMed, Web of Science, and Cochrane Library databases.
The following search terms were used: “survivin”; and “Colorectal cancer”, and “CRC”. The searched studies were limited to the English and Chinese.

Inclusion and exclusion criteria

All the studies identified were reviewed independently by two investigators and the studies were included if they fulfilled the following criteria: (1) a case-control study or cohort study was reported; (2) the cases were diagnosed as CRC and the control group was composed of healthy individuals; (3) the genotypes of survivin -31 G/C polymorphism were described in the studies. The references were excluded from the meta-analysis as follows: (1) the study was not related to CRC; (2) the reference did not describe genotypes of the survivin -31 G/C polymorphism in the two groups; (3) the reference consisted of duplicate data or publications from the included studies.

Data extraction

The following data were recorded from each article: first author, years of publication, ethnicity, gender, age, numbers of subjects, site of CRC, stage of CRC, smoke and drink status. The data were extracted by two of the authors independently. Discrepancies between these two authors were resolved by discussion.

Quality assessment

Quality assessment was conducted for each article according to Strengthening the Reporting of Genetic Association studies (STREGA) [11] containing eleven items associated with valid data reported in the study. For each item, there are three degrees, “yes” (scored 2), “can’t tell” (scored 1) or “no” (scored 0), after evaluating each item, a total score from 0 to 22 was reported for each article. Studies would be divided into 3 grades: Grade A (scored 15-22, high quality), Grade B (scored 8-14, medium quality), or Grade C (scored 0-7, inferior quality). Only the studies of Grade A or B would be included in the final analysis.

Statistical analysis

Stata 12 software was used to calculate the pooled odds ratios (ORs) with 95% confidence intervals (CIs) based on the available data from each article. \( P < 0.05 \) was considered statistically significant. The recessive model was estimated. Cochran's Q-statistic and the \( I^2 \) test were used to test the heterogeneity among the included studies, and \( P < 0.1 \) and \( I^2 > 50\% \) suggested significant differences in study heterogeneity. When significant heterogeneity was observed across studies, the pooled results were based on random effects models. The \( \chi^2 \) test was applied to assess whether the genotype distributions of the control populations conformed to Hardy-Weinberg equilibrium (HWE), and \( P < 0.05 \) was considered statistically significant. Begg's funnel plot and Egger's test were used to detect publication bias.

Results

Study characteristics

In our study, we initially searched 54 related references, among which 12 were duplicates. When removing the duplicates and other unrelated references, 6 references met our inclusion criteria and were recruited in the meta-
analysis (Figure 1). The information of the included studies were listed in Table 1. There were 2644 subjects, including 1840 cases with CRC and 1804 controls. All studies received a score of more than or equal to 17, indicating good quality.

**Results of meta-analysis**

The results of the association between survivin -31 G/C polymorphism and CRC risk are summarized in Table 2. Survivin -31 G/C polymorphism was associated with a significantly increased risk of CRC (OR = 1.78; 95% CI, 1.53-2.07; $I^2$ = 0%; Figure 2). In the race subgroup analysis, both Asians (OR = 1.72; 95% CI, 1.44-2.05; $I^2$ = 0%) and Caucasians (OR = 1.93; 95% CI, 1.46-2.55; $I^2$ = 0%) with survivin -31 G/C polymorphism had increased CRC risk. In the subgroup analysis according to site of CRC, survivin -31 G/C polymorphism was not associated with colon cancer risk (OR = 2.02; 95% CI, 0.79-5.22; $I^2$ = 82%). However, this polymorphism was significantly associated with rectum cancer risk (OR = 1.98; 95% CI, 1.42-2.74; $I^2$ = 0%). In the subgroup analysis by clinical stage, both early stage (I+II) and advanced stage (III+IV) were associated with survivin -31 G/C polymorphism (OR = 1.61; 95% CI, 1.20-2.16; $I^2$ = 0% and OR = 2.30; 95% CI, 1.70-3.13; $I^2$ = 0%, respectively). In the subgroup analysis by smoke status, both smokers and non-smokers with survivin -31 G/C polymorphism showed increased CRC risk (OR = 1.47; 95% CI, 1.01-2.13; $I^2$ = 60% and OR = 1.71; 95% CI, 1.28-2.30; $I^2$ = 0%, respectively). In the subgroup analysis by drink status, both drinkers and non-drinkers with survivin -31 G/C polymorphism showed increased CRC risk (OR = 1.58; 95% CI, 1.06-2.37; $I^2$ = 8% and OR = 1.61; 95% CI, 1.23-2.11; $I^2$ = 0%, respectively).

Figure 3 showed the Egger’s publication bias plot in the meta-analysis. The plots shape, as well as the $P$ value from Egger’s regression ($P = 0.655$), did not show evidence of publication bias.

**Discussion**

In this meta-analysis, we investigated the association between the survivin -31 G/C polymorphism and CRC risk including 1840 cases with CRC and 1804 controls. We found that individuals with survivin -31 G/C polymorphism showed an increased risk of CRC in the overall population. In the stratified analysis by ethnicity, the significant association was observed in Asians...
Survivin and CRC

and Caucasians. In the stratified analysis by site of CRC, survivin -31 G/C polymorphism significantly increased rectum cancer risk, but not colon cancer risk. We found significant heterogeneity in colon cancer risk. Thus, more studies with colon cancer risk are still needed. In the subgroup analysis by stage of CRC, smoking status and drink status, positive results were found in all these subgroup analyses.

Kim et al. found that survivin was a candidate biomarker for the prediction of recurrence and survival in CRC [12]. Goossens-Beumer et al. also suggested that identified combined expression levels of Aldh1, Survivin, and EpCAM as strong independent prognostic factors, with high hazard ratios, for survival and tumor recurrence in colon cancer patients [13]. A recent meta-analysis revealed a positive correlation between survivin expression and poor prognosis in CRC [14]. In addition, that meta-analysis revealed a significant association between expression of survivin and the presence of lymph node metastases or blood vessel invasion [14]. Functionally, survivin exhibits distinct functions during cell cycle progression or as inhibitor of programmed cell death together with IAP-family member XIAP, by promoting stability of XIAP and synergistically inhibition of caspase-9 [15]. In addition, survivin promotes by complexing XIAP invasion and migration of malignant cells via NF-κB pathways, apparently contributing to metastasis [16].

Surviving also contributed to other cancers. Javid et al. demonstrated that survivin (-31G > C) was associated with significantly increased survivin gene expression and ultimately may contribute in the poor clinical outcome of non-small cell lung cancer patients [17]. Aminimoghad-

dam et al. observed survivin rs9904341C allele was associated with increased endometrial carcinoma risk [18]. Chen and colleagues suggest that the high survivin expression was associated with tumor stage and grade and may present a predictive marker of overall survival in urothelial carcinoma [19].

Some limitations should be addressed. First, only published English and Chinese language studies were included in this meta-analysis, so the language bias might influence the results. Second, the sample sizes in several of the incorporated studies were relatively small, which may reduce the strength of our conclu-
survivin -31 G/C polymorphism may be associated with the risk of CRC.

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Disclosure of conflict of interest

None.

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