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Review

Prognostic role of serum total cholesterol and high-density lipoprotein cholesterol in cancer survivors: A systematic review and meta-analysis

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ABSTRACT

Background: The alterations of lipid profile in cancer has been reported to be associated with cancer development. However, the prognostic value of serum lipid markers level in cancer is currently under debate. Here we performed a meta-analysis to investigate the prognostic significance of serum blood total cholesterol (TC), Triglycerides (TG), high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) for cancer.

Methods: We systematically searched in PubMed and EMBASE for follow-up studies to evaluate the association between blood TC, TG, HDL-C, LDL-C and overall survival (OS) or disease-free survival (DFS) in patients with cancer. Pooled hazard ratio (HR) and 95% CIs were pooled using the random models. Subgroup and sensitivity analyses were also performed.

Results: Twenty-six studies including 24655 individuals were identified. For patients with higher TC before diagnosis, the summary HR were 0.82 (95% CI 0.75–0.90) for OS, 0.920 (95% CI, 0.849–0.997) for DFS. Patients with higher HDL-C had a 37% reduced risk of death compared with lower HDL-C (HR 0.63, 95%CI 0.47–0.86, $P < 0.001$). As for DFS, patients with higher HDL-C level had the risk of disease relapse reduced by 35% (HR 0.65, 95% CI, 0.48–0.89, $P < 0.001$) compared with patients with lower levels.

Conclusions: After pooled analysis, only TC and HDL-C were significantly associated with cancer survival. Our findings demonstrate for the first time that serum TC and HDL-C was identified as a protective factor for overall survival in cancer patients.

1. Introduction

Advances in understanding mechanisms underlying cancer biology have resulted in the identification of novel therapeutic targets that have prolonged the lives of some patients with cancer. Nevertheless, stratifying risk before giving treatments remain significant challenges for oncologists. Clinicians currently relies exclusively on the TNM staging system based on preoperative imaging or biopsy to do risk stratification [1–6], which cannot always accurately predict the benefit from therapy and risk of disease recurrence in cancer patients [7,8]. Therefore, finding new prognostic biomarkers which can contribute to better stratify cancer risk and select patients who can most benefit from treatments could be especially useful.

Currently, abnormal lipid metabolism is increasingly recognized as important mechanism of carcinogenesis, and it has been widely evaluated that disorders in lipid and lipoprotein metabolism as a result of metabolic syndrome, overweight and obesity, might be associated with cancer risk and impacts prognosis in cancer patients [9–11]. Cholesterol, localized in lipid rafts-membrane micro-domains, assembles the signal transduction machinery and cell biological studies support a critical involvement of cholesterol in the modulation of proteins implicated in key cellular signaling pathways. These pathways organization can result in malignant transformation, including breast, colon, and nasopharyngeal cancer, due to altered cytoskeleton, cell polarity and angiogenesis [12–19]. However, the clinical data on cancer remains very limited and inconsistent. Several studies support the positive association between high level of total cholesterol (TC) and cancer incidence [20–22] and overall mortality in cancer patients [23]. On the contrary, no association or even inverse association between TC levels and incidence of cancer was observed [24–27].

High and low density serum lipoproteins act as key lipoprotein carriers of cholesterol to cancer cells via receptor mediated mechanisms

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[28]. In addition, they also play an important role in regulating the signaling pathways of cancer cell. It was reported that low density lipoproteins (LDL) can promote cancer metastasis through regulating integrin transfer [29,30]. It also has been found that patients with distant metastases had markedly higher levels LDL-C compared with patients without metastases [31]. However, retrospective studies have revealed that patients with lower LDL-C levels are associated with a greater risk of malignancy [32,33]. Recent studies have investigated that serum high-density lipoprotein (HDL) is associated with the incidence of cancer especially breast cancer. These findings imply that HDL might play an important role in promoting tumor progression [34–36]. However, the exact mechanism of lipid metabolism in tumor development has not been completely stated. Previous research has reported that low HDL-C levels are in relation to increased post-menopausal breast cancer risk [37–39]. In addition, reduced pre-treatment HDL-C levels were associated with worse prognosis in NSCLC patients [40].

Given the substantial controversy in various cancers, such as breast cancer, gastric cancer, lung cancer, hepatocellular carcinoma and renal cell cancer, we perform a meta-analysis to investigate the prognostic values of the serum lipid parameters, including HDL-C, LDL-C, TC, and Triglyceride (TG) in cancer patients. To our knowledge, our study is the first meta-analysis to make research about the association of TC, TG, LDL-C, and HDL-C with oncologic outcomes in cancer.

2. Methods

2.1. Search strategy

We performed a systematic literature search, limited to publications in English, for the studies about the association between pretreatment lipid profiles and OS or DFS in patients with cancer through PubMed and EMBASE databases between January 1984 and 8 October 2017. The search strategy contained free-text words and Medical Subject Headings (MeSH)/EMTREE terms: “cancer”, “cholesterol”, “Triglycerides (TG)”, “lipoprotein” and “survival”, “mortality” or “prognosis”. The references of all relevant studies, reviews and meta-analysis papers were hand-searched for additional records that were not identified through database search.

2.2. Eligibility criteria

Two reviewers (ZPT and LB) independently selected the appropriate studies based on the title and abstract screening and retrieved full text publications using the criteria outlined below to identify eligible studies. Studies were included in this meta-analysis if all of the following criteria were met: (i) studies published as an original article in a peer-reviewed journal; (ii) studies reporting on the outcome measures, such as OS or DFS; and (iii) studies evaluating the prognostic impact of the serum TC, TG, HDL-C and LDL-C in various cancer and providing relevant patient survival data with a hazard ratio (HR) estimate and its 95% confidence interval (CI), or indirect information such as Kaplan-Meier curves used to estimate survival data based on the methods previously described [41]. Study exclusion criteria were studies of lipid profiles detection in blood by Mass spectrum; and papers that did not report adequate information to assess study methods for risk of bias or to determine study eligibility are also excluded. When more than one publication reported on the same population or overlapping populations, only the study with the largest sample size or the most informative one was selected into the meta-analysis. If studies did not own complete data to calculate HRs, we contact the corresponding author by email to request this information.

2.3. Data extraction and quality assessment

Two data extractors reviewed eligible studies and collected the following information, independently. The following data were extracted: the name of the first author, study design, country, year of publication, cancer type and stage, patient age, research country, cutoff value of TC, TG, HDL-C and LDL-C, inclusion period, follow-up duration, adjustment variables, outcome type and HR estimates (with the corresponding 95% CIs) for lipid profiles in cancer. For each study, we assessed the quality of the evidence included using the Newcastle-Ottawa Quality Assessment Scale [42]. On a score scale from 0 to 9, a study with 7 or higher was considered as high-quality.

2.4. Statistical analysis

The prognostic effect of different levels of TC, TG, HDL-C and LDL-C in cancer was evaluated by HR and corresponding 95% CI. If the HRs and 95% CIs were reported in the study, we retrieved from the original studies directly, or they were calculated from available data using Engauge Digitizer version 4.1 [43]. Subgroup analyses were performed to investigate the associations of lipid profiles according to baseline features such as cancer type, country, publication type, et al. to explore the potential source of heterogeneity.

Because different cancer type analyses were used across studies, we expected heterogeneity in study estimates of the lipid level effect on survival, and thus we applied a random-effects model to estimate the HR [44]. The heterogeneity among the studies was assessed by the Cochran's Q-test and I^2 statistic. $I^2 < 50\%$ and $P > 0.05$ indicated no significant heterogeneity and pooled HR was estimated using fixed-effects model. Otherwise, a random-effects model was adopted. To evaluate the stability of the results, a one-way sensitivity analysis was performed to evaluate the influence of individual studies by estimating the average HR in the absence of each study. Publication bias was assessed by visual inspection of the contour-enhanced funnel plot symmetry as well as by Begg's regression and Egger's linear regression method [45,46]. When publication bias was emerged, we performed a “trim and fill” method to further analyses the possible influence of publication bias in our study [47].

All analyses were performed using Stata version 12.0 (Stata Corporation, College Station, TX, USA), and statistical significance was considered when A two-sided P value was < 0.05.

3. Results

3.1. Search and selection of studies

A flow diagram of the articles selection process is shown in Fig. 1. A total of 63 publications assessing the relationship of lipid profiles and cancer mortality were identified. Among them, 37 studies, including four studies on other lipid markers, 10 publications without a measure of survival association, 5 publications on the impact of various treatments on markers and 18 publications reported statistically significant increased risk of cancer morbidity, were excluded. Finally, 27 comparisons from 26 studies with 24,655 participants were included in the meta-analysis for extracting data and qualitative synthesis, of which 20 studies for TC [23,35,48–65], 11 studies for TG [23,35,48,51,55–57,59,60,63,66], 11 studies for HDL-C [35,36,48,49,51,55,57,59,63,66,67] and 12 studies for LDL-C [35,48,49,51,55,57,59,63,68–71].

3.2. Study characteristics

Clinical characteristics of the studies eligible for assessment are reported in Table 1. The studies were done between 1985 and 2016 in 10 countries. Most of the studies were based in Asian or North America. There were fourteen studies from China, three studies from Korea, two studies form USA, one studies form Japan and six international studies. Follow-up of patients with cancer were performed in five prospective studies including 3253 individuals or twenty-one retrospective studies including 21,402 patients. Stage of tumor at diagnosis and patient cancer characteristics varied across studies. Some studies included only