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Meta-analyses

Association of choline and betaine levels with cancer incidence and survival: A meta-analysis

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SUMMARY

Background & aims: Evidences suggest possible link between betaine and choline, methyl group donors, and cancer progression. We examined the association between choline and betaine levels and cancer incidence and survival in a meta-analysis of observational studies.

Methods: We identified observational studies examining the association between choline and/or betaine levels from diet or blood and cancer incidence and survival by searching the PubMed and Web of Science databases for studies published up to Jan, 2018. After applying the selection criteria, 28 observational studies (9 case-control, 1 cross-sectional, and 18 cohort studies) were included. Relative risks (RR) and 95% confidence intervals (CI) were extracted, and combined RRs were calculated using random-effects models.

Results: Choline levels were not associated with cancer incidence in a meta-analysis of cohort studies. Betaine levels reduced the risk of cancer incidence in a meta-analysis of cohort studies; combined relative risks (RRs) (95% CIs) comparing the top with the bottom categories were 0.93 (0.87–0.99). When we analyzed separately according to exposure assessment method, combined RRs (95% CIs) comparing the top with the bottom categories of betaine levels were 0.87 (95% CI: 0.78–0.95) for dietary betaine and 0.88 (95% CI: 0.77–0.99) for blood levels of betaine. There were no significant associations with cancer survivorship of choline or betaine levels.

Conclusions: We concluded that high betaine levels were associated with lower risk of the cancer incidence, especially for colorectal cancer.

1. Introduction

Choline, which is essential for integrity of cell membrane structure, signaling functions of cells, and synthesis of neurotransmitters, is available as free choline, phosphocholine, glycerophosphocholine, sphingomyelin, or phosphatidylcholine [1]. Furthermore, choline is a precursor of betaine and acetylcholine, which is an important neurotransmitter in the processes of memory storage, muscle control, and various other functions [1]. Along with folate and other B vitamins, choline and betaine take part in one-carbon metabolism, which constitutes a network of integrated biochemical pathways transferring one-carbon (methyl) groups between compounds [2]. Betaine and folate are methyl-group donor for homocysteine that is converted to methionine with assistance from betaine homocysteine methyltransferase (BHMT) and methionine synthase (MTH). Methionine transfers a methyl-group to S-adenosylmethionine (SAM) which donates methyl group to DNA and RNA [3]. DNA methylation, which is a genetic alteration of gene function that occurs without changes to the sequence of DNA, is an important determinant in the development of cancerous cells, and has been implicated in gene expression, conservation of DNA integrity and firmness, chromatin alteration, and mutation [4].

Epidemiological evidence regarding the role of dietary choline and betaine in cancer development and progression has accumulated in last ten years following the advent of a food composition database for choline and betaine in 2003 [5,6]. Given the lack of comprehensive systematic reviews of the role of choline and

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betaine in cancer development, we investigated the associations between choline or betaine and cancer incidence and survival by performing a meta-analysis of observational epidemiological studies.

2. Materials and methods

We followed the Meta-analysis Of Observational Studies in Epidemiology guidelines [7].

2.1. Search strategy

Searching the PubMed and Web of Science databases for studies published up to January 22, 2018, epidemiological studies investigating the association between choline and/or betaine and cancer were identified. A single author (J Youn) performed the systematic search and another author (JE Lee) checked the extracted studies. We used the following search terms: “choline or betaine or one-carbon metabolite or one-carbon metabolism” and “intake or diet or serum or plasma or circulating” and “cancer or carcinoma or neoplasia or adenoma” in PubMed; and “choline or betaine” and “intake or diet or serum or plasma or circulating” and “cancer or carcinoma or neoplasia or adenoma” in Web of Science. We used a filter function of PubMed and limited the search to “Human” in species and “English” in languages. For Web of Science, we refined the searches to “Articles” in document types and “English” in languages. We also checked the reference lists from all retrieved journals in order to include additional relevant studies.

2.2. Inclusion criteria

Studies were included in our meta-analysis if they met the following criteria: 1) the exposure of interest was choline and/or betaine, which was assessed using dietary or biochemical analyses; 2) the endpoint of interest was cancer incidence or mortality; 3) relative risk (RR) estimates and 95% confidence intervals (CIs) were provided for the associations between choline and/or betaine levels and incidence and/or mortality of any cancer; 4) the study was designed as an observational study; and 5) the study was published in English.

2.3. Data extraction

We extracted the following information from each study: the first author's full last name and initial of the first name; publication year; country of the study population; study design; study period; sex of study population; outcomes (cancer types or deaths); the number of cases and controls for case-control studies, and the incidence and total person-years for cohort studies; estimate parameters (RRs, odds ratio or hazard ratio); 95% CIs; ranges and/or medians of each category; type of exposure assessment (dietary or biochemical); and covariates adjusted in multivariate models. The quality of each study was assessed using selected items of “strengthening the reporting of observational studies in epidemiology” [8]. For case-control and cross-sectional studies, we assessed adjustment for confounding factors and the sources and methods of case ascertainment, control selection, recall bias, and assessment of exposures, outcomes and covariates. For cohort studies, we assessed whether important confounding factors were adjusted for, how loss to follow-up was addressed, and how endpoint was measured.

2.4. Statistical analysis

The combined RRs and 95% CIs for the top choline or betaine categories, as compared with the bottom categories, were calculated using the random effects model [9]. Weight was given to individual studies depending on the inverse proportion of variances. Heterogeneity among studies was examined using the I^2 statistic, where $I^2 = 100\% \times (Q - df)/Q$, where Q is Cochran's heterogeneity statistic and df is the degrees of freedom [10,11]. A sensitivity analysis was performed to identify the influence of the RRs by excluding studies has heterogeneous results, such as Chinese studies. Furthermore, a subgroup analysis and meta-regression analysis [12,13] using the natural logarithm of the RR from each study were conducted to evaluate whether the associations between choline or betaine and cancer differed according to the type of exposure assessment, sex, geographic region (Australia, Europe, and the US and China and Singapore), or study design (case-control and cohort). When reported [14–22], or when investigators provided estimates by folate levels [17,19,20,23–25], whether the association between choline or betaine and cancer differed according to folate intake (low and high) was investigated.

To assess the dose-response association between choline or betaine levels and cancer incidence, we estimated the RR per 50 mg/d increase for choline or betaine intake and the RR per 5 μmol/L increase for circulating choline or betaine levels by regressing the log RRs using generalized least squares [26]. Authors were contacted, or our previous studies were reviewed, to obtain information regarding the number of cases or person-years according to categories, or the median of each category, which are required for a dose-response analysis [19,23–25,27–31]. We used the median of each category in the dose-response analysis. We assumed that the level had the same amplitude as the neighboring categories if the bottom or top category was open-ended. We examined the publication bias using a funnel plot and Egger's test [32]. $p < 0.10$ was considered indicative of departure from no publication bias. Statistical analyses were performed with the STATA 15 statistical software (Stata corp. College Station, TX, USA). Two-sided p-values of <0.05 were considered statistically significant.

3. Results

3.1. Publication identification

A total of 1526 papers were extracted from PubMed and Web of Science, of which 1495 were excluded for the following reasons: 1343 did not examine the association between choline and/or betaine and cancer; 131 were reviews; two were books; eight were case reports; and eleven were editorial commentaries. Of the 31 articles that were retrieved, four case-control studies included the same population [33–36]. We included one [33] out of four for both cancer incidence and survival analyses for the following reasons: the study included [33] was published after the publications of two studies [34,35]; and used conventional logistic models whereas the other study reported betaine and specific types of choline in pathway based-hierarchical regression models [36]. There were three studies [14,37,38] which included partly overlapped populations from the first and second stage case-control studies. Out of these three studies, we included the estimates from the first stage case-control study in the prior published study [14] and the second stage case-control study in the more recent study [37]. When we conducted the dose-response and meta-regression analysis by folate levels, we included the first and second stage case-control studies in the previous study [14], where the estimates by folate levels were available. The other study [38] was excluded because the serum choline and betaine levels were measured after ascertaining the cases, that is, the study did not demonstrated cancer prevention. In summary, a total of 4 studies were excluded out of 31 articles. One additional study was identified from the references of

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