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Review

Coffee and caffeine intake and breast cancer risk: An updated dose–response meta-analysis of 37 published studies

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HIGHLIGHTS

- Coffee and caffeine might be weakly associated with breast cancer risk for postmenopausal women.
- A strong and significant association was found for BRCA1 mutation carriers.

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ABSTRACT

Objective. We conducted an updated meta-analysis to summarize the evidence from published studies regarding the association of coffee and caffeine intake with breast cancer risk.

Methods. Pertinent studies were identified by a search of PubMed and by reviewing the reference lists of retrieved articles. The fixed or random effect model was used based on heterogeneity test. The dose–response relationship was assessed by restricted cubic spline model and multivariate random-effect meta-regression.

Results. 37 published articles, involving 59,018 breast cancer cases and 966,263 participants, were included in the meta-analysis. No significant association was found between breast cancer risk and coffee (RR $= 0.97$, $P = 0.09$), decaffeinated coffee (RR $= 0.98$, $P = 0.55$) and caffeine (RR $= 0.99$, $P = 0.73$), respectively. And the association was still not significant when combining coffee and caffeine (coffee/caffeine) (RR $= 0.97$, $P = 0.09$). However, an inverse association of coffee/caffeine with breast cancer risk was found for postmenopausal women (RR $= 0.94$, $P = 0.02$), and a strong and significant association of coffee with breast cancer risk was found for BRCA1 mutation carriers (RR $= 0.69$, $P < 0.01$). A linear dose–response relationship was found for breast cancer risk with coffee and caffeine, and the risk of breast cancer decreased by 2% ($P = 0.05$) for every 2 cups/day increment in coffee intake, and 1% ($P = 0.52$) for every 200 mg/day increment in caffeine intake, respectively.

Conclusions. Findings from this meta-analysis suggested that coffee/caffeine might be weakly associated with breast cancer risk for postmenopausal women, and the association for BRCA1 mutation carriers deserves further investigation.

Contents

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Introduction

Breast cancer is the one of the most frequently diagnosed cancer in women, and ranks second as a cause of cancer death in women (after lung cancer) [1]. An estimated 226,870 new cases of invasive breast cancer, 63,300 new cases of in situ breast cancer and 39,510 breast cancer deaths are expected among women in the US during 2012, and the breast cancer incidence rates are stable since 2004 [1]. Coffee is one of the most popular beverages in the world, and the latest coffee trade statistics estimated that world coffee export amounted to about 6.76 billion kg in 2011/2012 [2]. The association between coffee intake and breast cancer risk has been investigated since the early 1970s [3], and many epidemiologic studies have been published on coffee or caffeine intake and breast cancer risk. However, according to the World Cancer Research Fund/American Institute for Cancer Research in 2008, the result was still inconclusive on coffee intake and breast cancer risk for both premenopausal and postmenopausal women [4]. A meta-analysis is available on coffee intake with breast cancer risk [5]. 10 studies (8 cohort studies [6–13] and 2 case–control studies [14,15]) were published thereafter, and we additionally identified10 studies (1 cohort [16] and 9 case–control studies [17–25]) that were published before the meta-analysis. The association of caffeine intake with breast cancer risk is not summarized, and the association of coffee intake with breast cancer risk by menopausal status, body mass index (BMI), estrogen receptor (ER) and progesterone receptor (PR) status, breast cancer stage, and adjustment for important clinical and lifestyle factors is still unknown. Besides, the dose–response relationship, which is essential for proving causality, is also unknown. In addition, categories of coffee and caffeine intake levels differed between studies, which might complicate the interpretation of the pooled results across study populations with different categories. In this respect, a dose–response meta-analysis with restricted cubic spline functions provides a solution to the problem. Therefore, we conducted an updated dose–response meta-analysis to explore the above-mentioned issues in this study.

Methods

Literature search and selection

We performed a literature search up to Dec 2012 using PubMed database with the key words coffee or caffeine combined with breast cancer without restrictions. Furthermore, the reference lists of retrieved articles were scrutinized to identify additional relevant studies.

Two investigators independently reviewed the identified studies, and studies were included if they met the following criteria: (1) the study was conducted in humans; (2) the exposure of interest was coffee or caffeine; (3) the outcome of interest was breast cancer; and (4) relative risk (RR) with 95% confidence interval (CI) was provided (we presented all results with RR for simplicity). For dose–response analysis, the study had to report RR (95% CI) for at least 3 quantitative categories of coffee or caffeine intake. Besides, the number of cases and participants or person-years for each category of coffee or caffeine intake must be also provided (or data available to calculate them). If data were duplicated in more than one study, we included the study with the largest number of cases.

Data extraction

The following data were extracted from each study by two investigators: the first author's last name, publication year, the name of the cohort study, country where the study was conducted, years of follow-up, age, sample size (number of cases and total number of participants), coffee and caffeine intake categories, covariates adjusted for in the multivariable analysis, and the RRs with their 95% CIs for each category of coffee and caffeine intake. We extracted the RRs that reflected the greatest degree of adjustment for potential confounders. For dose–response analysis, the number of cases and participants (person-years) for each category was also extracted. The median or mean level of coffee and caffeine intake for each category was assigned to the corresponding RR for every study. If the upper boundary of the highest category was not provided, we assumed that the boundary had the same amplitude as the adjacent category [26].

Statistical analysis

Pooled measure was calculated as the inverse variance-weighted mean of the logarithm of RR (95% CI) of breast cancer for the highest versus lowest category of coffee and caffeine, respectively. The I^2 of Higgins and Thompson was used to assess heterogeneity [27]. I^2 is the proportion of total variation contributed by between-study variation, and I^2 values of 0, 25, 50, and 75% represent no, low, moderate, and high heterogeneity [27], respectively. If moderate or lower heterogeneity ($I^2 < 50\%$) was found, the fixed effect model (FEM) was used as the pooling method, otherwise, the random effect model (REM) was adopted ($I^2 > 50\%$) that considers both within-study and between-study variations. A sensitivity analysis was performed with one study removed at a time to assess whether the results could have been affected markedly by a single study. Publication bias was evaluated using the Egger regression asymmetry test. Subgroup analysis was performed by study design (cohort study or case–control study), follow-up duration for cohort study (<10 years or >10 years), source of controls for case–control study (population-based or hospital-based), menopausal status (premenopausal or postmenopausal), ER and PR status (ER+PR+, ER+PR−, ER−PR+ or ER−PR−), BMI (<25 kg/m^2 or >25 kg/m^2), breast cancer stage (in situ or invasive) and country where the study was conducted (USA, Europe or Asia). Besides, subgroup analysis was also performed by adjustment (yes or no) for smoking and/or alcohol, BMI, total energy intake, physical activity, oral contraceptive use, postmenopausal hormone replacement therapy use, family history of breast cancer and history of benign breast disease.

For dose–response analysis, a two-stage random-effects dose–response meta-analysis [28] was performed to compute the trend from the correlated log RR estimates across levels of coffee and caffeine, respectively, taking into account the between-study heterogeneity. In the first stage, a restricted cubic spline model with three knots at the 25th, 50th, and 75th percentiles [29] of the levels of coffee and caffeine, was estimated using generalized least square regression taking