Original Article

The association between coffee intake and breast cancer risk: a meta-analysis and dose-response analysis using recent evidence

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Background: To assess the association between coffee intake and breast cancer risk using data from studies published during the past 15 years.

Methods: Articles published between January 2005 and May 2020 were collected from PubMed, Embase, and Web of Science databases, and the Cochrane library. Coffee consumption was set as the exposure factor of breast cancer risk, and relative risk (RR) was set as the assessment indicator. Random-effects or fixed-effects models were used for the meta-analysis, depending on the level of heterogeneity. The linear and non-linear dose–response relationship was assessed using the generalized least-squares method and restricted cubic spline model. Articles were evaluated by sensitivity analysis, and Begg's and Egger's tests and funnel plots were used to evaluate publication bias. The process of meta-analysis referred to Meta-analyses of Observational Studies in Epidemiology (MOOSE).

Results: We retrieved 26 relevant studies in the dose–response analysis and meta-analysis. A negative correlation was found between coffee consumption and breast cancer risk (RR: 0.95; 95% CI: 0.92–0.99). A linear and marginal dose–response relationship was found for six case-control studies (RR: 0.98; 95% CI: 0.95–1.00) and 10 cohort studies (RR: 0.98; 95% CI: 0.97–1.00). Subgroup analysis showed that the relationship between coffee consumption and breast cancer risk was moderated by menstrual status and geographic region.

Conclusions: Overall, the meta-analysis found a negative correlation between coffee intake and breast cancer risk, especially in postmenopausal and European women.

Keywords: Coffee; breast cancer; dose–response; meta-analysis

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Introduction

Breast cancer is the most common type of malignancy in females (1). According to According to Ahmad, breast cancer statistics, breast cancer is the leading cancer among women, and the morbidity and mortality are increasing year by year (2). Certain factors affect the risk of breast cancer. One study shows that a high body mass index (BMI) is positively associated with the risk of breast cancer (3). Another study reports that women who have fewer children or have not breastfed have a higher risk of breast cancer (4). However, there remain some factors contributing to breast cancer that require elucidation.

It is thought that coffee, a common item consumption, may reduce the risk of type 2 diabetes mellitus and Parkinson's disease (5). Polyphenols and diterpenoids in coffee have been reported to have anti-inflammatory, antioxidant, and apoptotic properties (6). The consumption

of coffee has also been weakly associated with cardiovascular and cancer mortality (7), and it has been found that the daily consumption of coffee may reduce the recurrence rate of breast cancer (8).

Several studies have assessed the relationship between coffee and breast cancer risk, mainly using extreme intake or dose–response calculations (9-11). A meta-analysis of 20 case-control studies and 17 cohort studies calculated a relative risk (RR) of 0.97 (95% CI: 0.93–1.00), and a linear relationship was established for coffee consumption and breast cancer risk, which decreased by 2% for every two cups consumed per day (12). A concurrent meta-analysis of 16 cohort studies and 10 case-control studies found a marginally significant correlation between coffee and breast cancer (RR: 0.96; 95% CI: 0.93–1.00) (13). A more recent dose–response meta-analysis of 21 cohort studies found that in post-menopausal women, drinking four cups of coffee per day could reduce the risk of cancer by 10% (RR: 0.90; 95% CI: 0.82–0.99) (14). These data imply that coffee may exert a protective effect in some populations. However, the results of some recent studies, which were not included in these meta-analyses, contradict their outcomes. One study, for example, shows that instant coffee has a positive association with breast cancer risk (15), and another study shows that coffee and/or caffeine increases the risk of breast cancer among premenopausal or normal weight women (16). It is therefore necessary for us to include more recent studies in an analysis of the association between coffee and breast cancer risk. Recent case-control and cohort studies now enable us to perform subgroup analyses for menstrual status, BMI, and regional variance, as well as to compare their findings with those of older meta-analyses. We analyzed the literature on coffee consumption and breast cancer from the past 15 years to update the evidence for any association and to identify factors affecting this relationship. We present the following article in accordance with the PRISMA reporting checklist (available at http://dx.doi.org/10.21037/apm-20-1962).

Methods

Search strategy

We searched the PubMed, Embase, and Web of Science databases, and the Cochrane library, and limited the search to the period from January 2005 to May 2020. Keywords used in the search were “coffee”, “caffeine”, and “breast cancer”. To be eligible, a study had to meet the following criteria: (I) it was a case-control or cohort study; (II) it was conducted in humans; (III) the exposure of interest was coffee or caffeine; (IV) the outcome of interest was breast cancer; (V) the published data included RR, odds ratio or hazard ratio values after adjusting for confounders, and a corresponding confidence interval that could be extracted or calculated. The process of meta-analysis made reference to Meta-analyses of Observational Studies in Epidemiology (MOOSE).

Data extraction

The following information was extracted from each included study: first author’s last name, study design, case source or country where the study was conducted, follow-up duration, number of cases and subjects, adjustment for potential confounders, and coffee intake and the corresponding RR, odds ratio or hazard ratio, and 95% CI after adjusting for confounders from included studies. For each study, the minimum coffee consumption was set as the reference value for analysis, and the maximum coffee consumption was used as the exposure factor.

Assessment of study quality and risk of publication bias

The Newcastle-Ottawa Scale (NOS) evaluates study quality and the risk of bias from the selection of cases and controls, the comparability of cases and controls, and the ascertainment of exposure and non-response rates. We used the NOS for observational studies to assess the quality of the studies. Since the adjustment of different covariates in different included studies may affect the heterogeneity, we performed a subgroup analysis on the adjustment of different covariates, and the influence of each factor on the relationship between coffee consumption and breast cancer was verified by subgroup analysis (*Table 1*). For the measurement of coffee, in the dose-response meta-analysis, we used the regular coffee cup as the unit of measurement, and converted different measurement units into consistent units to reduce method heterogeneity. A sensitivity analysis was performed by excluding one study at a time to see whether this resulted in significant changes to the findings. A funnel plot, the Begg method, and the Egger’s test were used to assess publication bias.

Statistical analysis

RR, odds ratio, or hazard ratio for all coffee consumption

Table 1 Pooled measures of the association of coffee intake and breast cancer

Group	RR (95% CI)	P	I^2 (%)	Number of studies
Coffee type and caffeine				
Coffee	0.95 (0.92, 0.99)	0.199	18.3	24
Decaffeinated coffee	0.97 (0.91, 1.04)	0.869	0	8
Caffeine	0.94 (0.86, 1.03)	0.250	25.7	5
Geographic area				
North America	0.97 (0.91, 1.04)	0.129	33.7	10
Asia	1.01 (0.89, 1.14)	0.846	0	4
Europe	0.91 (0.86, 0.97)	0.454	0	8
Estrogen receptor (ER) status and progesterone receptor (PR) status				
ER+PR+	0.94 (0.87, 1.00)	0.375	7.1	7
ER-PR-	0.97 (0.85, 1.10)	0.373	7.4	7
Menopause status				
Premenopausal	0.98 (0.9, 1.06)	0.412	3.5	9
Postmenopausal	0.94 (0.89, 0.98)	0.516	0	9
Body mass index (BMI)				
≥25 kg/m^2	0.93 (0.83, 1.04)	0.902	3.5	3
<25 kg/m^2	1.05 (0.94, 1.16)	0.380	0	3
Adjustment for smoking				
Yes	0.96 (0.92, 1.00)	0.303	11.9	5
No	0.92 (0.83, 1.02)	0.130	41.3	19
Adjustment for alcohol				
Yes	0.96 (0.92, 1.00)	0.211	19.6	18
No	0.87 (0.75, 1.01)	0.349	10.6	6
Adjustment for BMI				
Yes	0.96 (0.91, 1.00)	0.319	12	18
No	0.94 (0.87, 1.02)	0.146	30.6	6
Adjustment for oral contraceptive (OC) use				
Yes	0.96 (0.90, 1.02)	0.388	5.8	18
No	0.95 (0.90, 1.00)	0.135	28.1	6
Adjustment for history of benign breast disease				
Yes	0.94 (0.87, 1.02)	0.391	2.8	5
No	0.95 (0.91, 1.00)	0.151	24	19

Relative risk (RR) in a random effects model was used for subgroup analysis. P value represents heterogeneity.

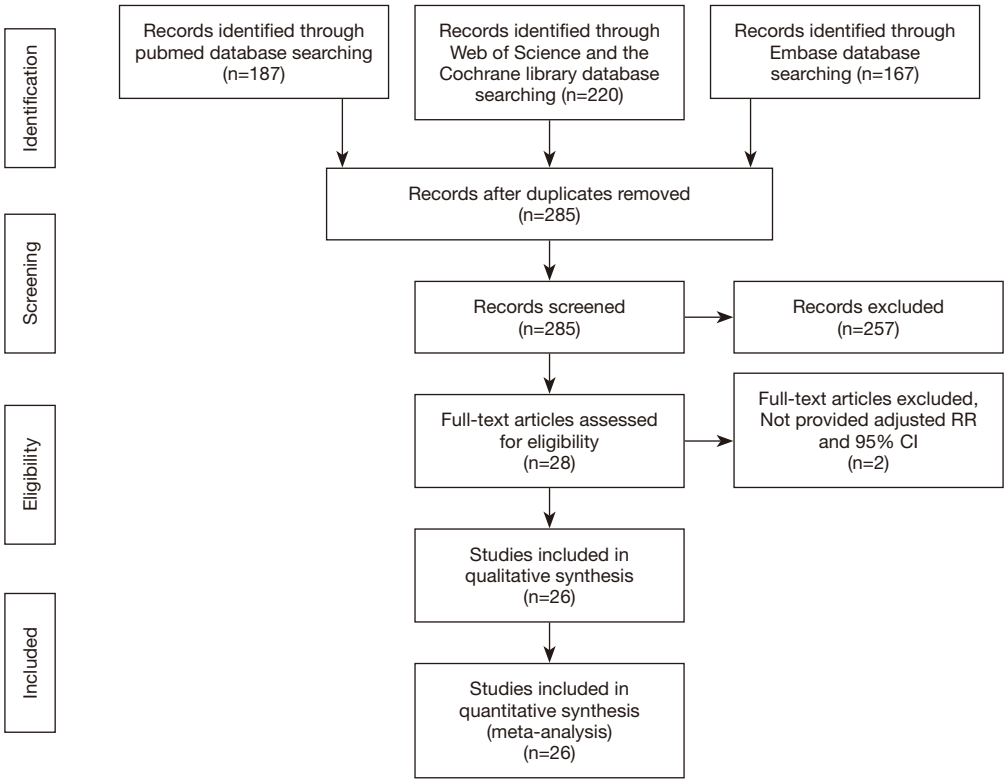

Figure 1 Flow chart of study selection. RR, relative risk; CI, confidence interval.

categories and breast cancer were extracted from each study. The RR and hazard ratio were considered equivalent measures of risk, and the odds ratio in case-control studies could also be approximated by the RR (17,18). The heterogeneity of effects between different studies was assessed by an I^2 statistical test or Q test, in which $I^2>50$ or $P<0.1$ for the Q test indicated significant heterogeneity. The random-effects model was used to analyze the effect values, taking into account the differences between the inside and outside of the study.

We also evaluated the dose–response relationship between coffee intake and breast cancer. We assigned the midpoint of the upper and lower boundaries in each category as the range of average intake. If the lower or upper boundary for the lowest and highest category, respectively, was not reported, we assumed that the boundary had the same amplitude as the closest category. The generalized least-squares method proposed by Greenland and Longnecker was used for dose–response analysis (19,20). In the first stage, the potential link between coffee intake and breast cancer risk was investigated by the restricted cubic spline model of four-section fixed-percentile (5%, 35%, 65%, and 95%) exposure distribution (21). In the next stage, the variance/covariance matrix and specific estimates (standard errors) were evaluated. The overall meaning of the curve was assessed by examining the joint effects of spline transformations. The P value of the non-linear curve was calculated using the null hypothesis of the second spline coefficient, which was equal to zero (12). All analyses were performed in Stata 14.0 (StataCorp, College Station, TX, USA); glst, xbls, and related packages were used for the analysis and graphing of the dose–response data.

Results

Article search and study characteristics

The search returned 285 articles from PubMed, Embase, and Web of Science databases and the Cochrane library, of which 257 were excluded (*Figure 1*). After the full texts of the 28 remaining articles were read, two were excluded for not providing a corrected RR value. *Table 2* lists the detailed characteristics of the final 26 articles that were included in the meta-analysis and dose–response analysis. All 26 articles measured coffee consumption, and five also

Table 2 Characteristics of studies in the meta-analysis on coffee consumption and breast cancer

Author, year	Study design follow-up (y)	Country, study name	Sample size (cases)	RR (95% CI) for highest *vs.* lowest category of coffee consumption	Adjustments
Baker, 2006 (22)	CC, –	USA, –	3,827 [1,932]	>4 *vs*. 0 cup/day, Premenopausal 0.62 (0.39–0.98)/Postmenopausal 0.99 (0.79–1.23)	Age, residence, and age at birth of first child
Gronwald, 2006 (23)	CC, –	Poland, –	696 [348]	Drinker *vs*. nondrinker 0.8 (0.5–1.1)	Year of birth age at diagnosis, age at menarche, parity, smoking, breast-feeding and OC use
Hirvonen, 2006 (24)	Cohort, 6.6	Finland, SU.VI. MAX	4,396 [95]	≥253 *vs*.111 ml/day 1.10 (0.66–1.84)	Age, smoking, number of children, OC use, FHBC and menopausal status
Nkondjock, 2006 (25)	CC, –	Four countries, –	1,690 [845]	≥6 *vs*. 0 cup/day 0.51 (0.26–0.98)	parity, smoking, OC use, alcohol, BMI at age 30
Hirose, 2007 (26)	CC, –	Japan, HERPACC	14,547 [2,122]	>3 *vs*. 0 cup/day 1.04 (0.85–1.28)	Age, year, motivation for consultation, parity, age at first delivery, smoking, drinking, type of breakfast, fondness of salty and fatty foods, fruit, vegetable, beef, fish, carrot, exercise and BMI
Kotsopoulos, 2007 (27)	CC, –	Canada, –	411 [170]	Drinker *vs*. nondrinker 0.61 (0.38–0.97)	year of birth, age at menarche, parity and smoking
Ganmaa, 2008 (28)	Cohort, 22	USA, Nurses' Health	85,897 [5,272]	≥6 cups/day *vs*. <1 cup/month 0.92 (0.82–1.03)	Age months, smoking, BMI, physical activity, height, alcohol, FHBC, HBBD, menopausal status,
Ishitani, 2008 (29)	Cohort, 10	USA, Women's Health Study	38,432 [1,188]	≥4 *vs*. 0 cup/day 1.08 (0.89–1.30)	Age, randomized treatment assignment, BMI, physical activity, energy, alcohol, multivitamin use, age at menopause, age at menarche, age at first pregnancy lasting atleast 6 months, number of pregnancies lasting at least 6months, menopausal status, postmenopausal hormone use, previous hysterectomy, previous bilateral oophorectomy, smoking, FHBC, HBBD
Larsson 2009 (30)	Cohort, 17.4	Sweden, Swedish Mammography	61,433 [2,952]	≥4 *vs*. <1 cups/day 1.02 (0.87–1.20)	Age, education, BMI, height, parity, age at first birth, age at menarche, age at menopause, OC use, use of postmenopausal hormones, FHBC, energy, alcohol and tea
Bissonauth, 2009 (31)	CC, –	Canada, –	560 [280]	>8 *vs*. ≤2 cups/day 1.4 (1.09–2.24)	Age, education, physical activity, smoking, coffee and energy
Wilson 2009 (32)	Cohort, 14	USA, Nurses' Health Study II	90,628 [1,179]	consumption level (5th *vs*. 1th) 0.92 (0.77–1.11)	BMI, height, OC use, parity and age at first birth, age at menarche, FHBC, HBBD, smoking, physical activity, animal fat, glycemic load, alcohol and energy
Boggs 2010 (33)	Cohort, 12	USA, Health-AARP Diet and Health study	52,062 [1,268]	≥4 *vs*. 1 cups/day 1.03 (0.77–1.39)	Age, energy, age at menarche, BMI at age 18, FHBC, education, geographic region, parity, age at first birth, OC use, menopausal status, age at menopause, HRT use, vigorous activity, smoking and alcohol

Table 2 (*continued*)

Table 2 (*continued*)

Author, year	Study design follow-up (y)	Country, study name	Sample size (cases)	RR (95% CI) for highest *vs.* lowest category of coffee consumption	Adjustments
Nilsson 2010 (34)	Cohort, 15	Sweden, Vasterbotten Intervention Project	64,603 [3,034]	≥4 *vs*. 1 cups/day 0.92 (0.68–1.25)	Age, sex, BMI, smoking, education and recreational physical activity
Bhoo, 2010 (35)	Cohort, 9.6	Netherlands, EPIC-NL	27,323 [681]	>5 *vs*. 0 cup/day 0.94 (0.72–1.24)	Age, smoking, education, BMI, alcohol, energy, saturated fat, fiber, tea, physical activity, OC use, presence of hypercholesterolemia, FHBC, age at menarche and parity
Li, 2011 (36)	CC, –	Sweden Germany, MARIE	5,929 [2,818] 8,046 [2,651]	>5 *vs*. ≤1 cups/day 0.84 (0.66–1.06) >5 *vs*. ≤1 cups/day 0.87 (0.71–1.07)	Age, HRT use, smoking, education and alcohol
Fagherazzi, 2011 (37)	Cohort, 11	France, E3N	67,703 [2,868]	>3 *vs*. 0 cup/day 1.02 (0.90–1.16)	Age, energy, OC use, age at menarche, age at menopause, number of children, age at first pregnancy, FHBC, education, HRT use, HBBD, menopausal status and BMI
Gierach, 2012 (38)	Cohort, 11	USA, Health-AARP Diet and Health study	198,404 [9,915]	Coffee:>4 *vs*. 0 cup/day 0.98 (0.91–1.07)	Age, race, education, BMI, smoking, alcohol, energy, age at first live birth, HRT use, history of breast biopsy and FHBC
Mizoo, 2013 (39)	CC, 0.9	Japan, –	936 [472]	≥4 *vs*. <1 cups/day 0.91 (0.55–1.51)	Age
Hashibe, 2015 (40)	Cohort, 13	Sweden, PLCO	50,563 [1,703]	≥2 cups/day *vs*. <1 cup/day; 0.97 (0.87, 1.08)	Age, sex, race and education, drinking frequency, alcohol
Oh, 2015 (41)	Cohort, 11	Sweden, Swedish Women's style and Health study	42,099 [1,395]	≥5 cups/day *vs*. ≤2 cups/day; 0.81 (0.70, 0.94)	Age, BMI, duration of breastfeeding, alcohol consumption
Harris, 2015 (42)	Cohort, 15	Sweden, SMC	37,004 [1,603]	Highest quartile *vs.* lowest quartile; 0.86 (0.72, 1.04)	Age, energy intake, height, BMI, education, OC use, HRT use, age at menarche, age at menopause, FHBC, HBBD smoking, physical activity, alcohol
Bhoo-Pathy, 2015 (43)	Cohort, –	Multicenter, EPIC	33,5060 [10,198]	Highest quartile *vs.* lowest quartile; premenopausal 1.00 (0.98, 1.03) postmenopausal 0.99 (0.98, 0.99)	Age at menarche, OC use, age at first delivery, ever breastfeeding, smoking, education, physical activity, alcohol, height, weight, energy intake from fat source, energy intake from non-fat source, total saturated fat intake, total fiber intake, ever-use of postmenopausal hormones
Kotemori, 2017 (44)	Cohort, 10	Japan, Japan Public Health Center-based (JPHC)	48,910 [792]	≥1 cups/day *vs*. <1 cup/week; 0.95 (0.77–1.18)	Age, area, BMI, FHBC, age at menarche, age at first delivery, number of deliveries, menopausal status and age at menopause, use of exogenous female hormones, smoking, alcohol

Table 2 (*continued*)

Table 2 (*continued*)

Author, year	Study design follow-up (y)	Country, study name	Sample size (cases)	RR (95% CI) for highest *vs.* lowest category of coffee consumption	Adjustments
Arthur, 2018 (16)	Cohort, 12.2	Canada, –	3,120 [922]	>4 *vs.* 0 cup 1.15 (0.83–1.58)	education, smoking, alcohol, BMI, total calories, physical activity, age at menarche, parity, breastfeeding, menopausal status, HRT use, OC use, FHBC
Yaghjyan, 2018 (45)	Cohort, 5.8	Yaghjyan, 2018 UK, –	126,182 [2,636]	>4 cups/day *vs.* <7 cups/week 0.98 (0.87–1.10)	Age, BMI, race, age at menopause, age at menarche, parity/ age at first birth, postmenopausal hormone use, FHBC, alcohol consumption, and smoking
Lee, 2019 (15)	CC, –	China, –	2,169 [1,156]	≥1 cup *vs.* 0 cup/day 1.09 (0.81–1.46)	age at interview, education, FBCH, HBBD, BMI, shift work experiences, smoking status, alcohol, tea, deep fried food, green vegetable consumption

BMI, body mass index; CC, case-control; CI, confidence interval; FHBC, family history of breast cancer; HBBD, history of benign breast disease; HRT, hormone replacement therapy; OC, oral contraceptive; RR, relative risk.

measured caffeine intake (29,33,40,41,45). Nine were case-control studies (15,22,23,25-27,31,36,39), and 17 were cohort studies.

Summary RR for the highest vs. lowest level of coffee consumption

As the EPIC study (43) included two study populations (35,37), we used it to analyze the relationship between coffee intake and breast cancer; the two populations were used only in the dose–response analysis. The overall RR for breast cancer of the highest *vs.* lowest coffee consumption categories was 0.95 (95% CI: 0.92–0.99), with low heterogeneity (I^2=18.3%, P=0.199) (*Figure 2*).

Subgroup analysis by population

We performed a stratified analysis by beverage type, geographic location, estrogen and progesterone receptor expression, menstrual status, and BMI (*Table 1*). In hierarchical analyses, coffee consumption and breast cancer risk were significantly and negatively correlated in European cohorts (RR: 0.91; 95% CI: 0.86–0.97) and in postmenopausal women (RR: 0.94; 95% CI: 0.89–0.98). No significant correlations were observed for other regions or for estrogen or progesterone receptor status, BMI, or beverage type.

Subgroup analysis by covariate

We also adjusted for the categorical covariates of smoking, alcohol consumption, use of oral contraceptives, and history of benign breast disease, and performed a stratified analysis (*Table 1*). No significant correlations were observed, with low to moderate inter-study heterogeneity (I^2<50%).

Dose–response analysis

Ten cohort studies were analyzed for dose–response relationships (28-30,33-35,37,38,41,46), with a pooled total of 26,868 cases of breast cancer. A linear relationship between coffee intake and breast cancer was observed (*Figure 3*, non-linear P=0.76). For every two cups of coffee consumed per day, the risk of breast cancer decreased by 2% (RR: 0.98; 95% CI: 0.97–1.00). The non-linear model (*Figure 4*) yielded similar results. Six case-control studies were also assessed (22,25,26,31,37,39), with 10,090 pooled cases of breast cancer (*Figure 5*, non-linear P=0.88). In this

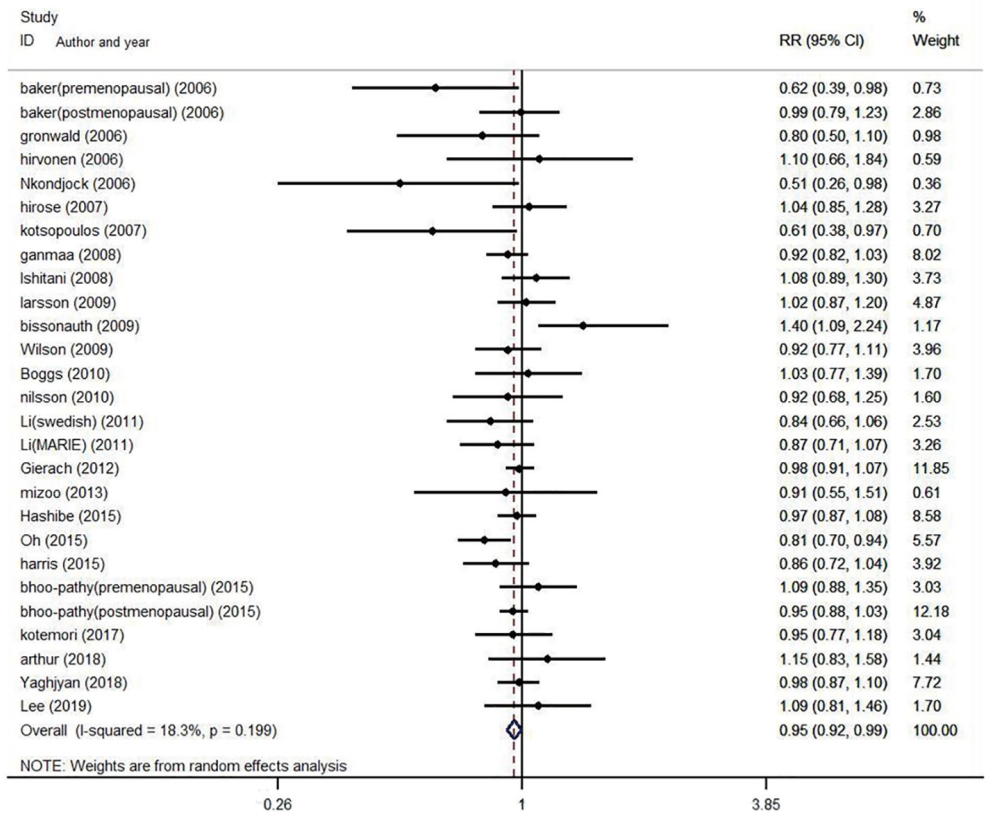

Figure 2 Multivariate-adjusted risk of breast cancer in the highest *vs.* lowest categories of coffee intake. CI, confidence interval; RR, relative risk.

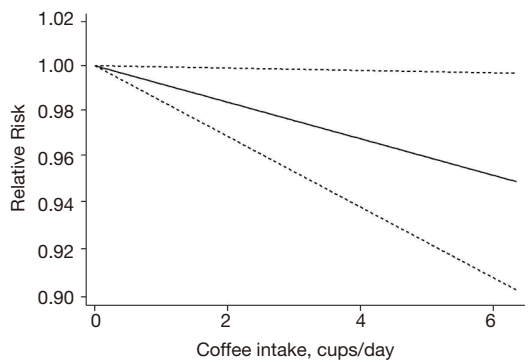

Figure 3 Relationship between coffee intake and breast cancer risk in a linear model (cohort study design).

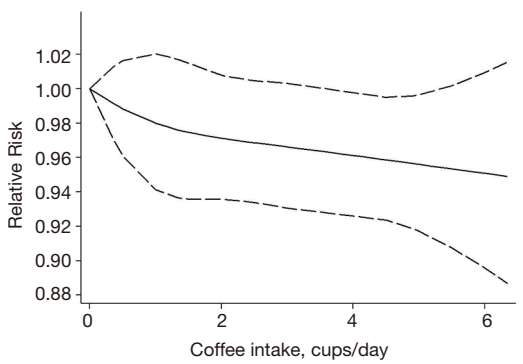

Figure 4 Relationship between coffee intake and breast cancer risk in a non-linear model (cohort study design).

analysis, for every two cups of coffee consumed per day, the risk of breast cancer decreased by 2% (RR: 0.98; 95% CI: 0.95–1.00). The results of the non-linear model (*Figure 6*) were similar. In summary, the case-control and cohort studies yielded consistent findings.

Study evaluation

All of the included studies were of high quality, according to the NOS. The sensitivity analysis (*Figure 7*) showed that no individual study had an excessive impact on the findings. The funnel plot (*Figure 8*) and Egger's test (*Figure 9*) found

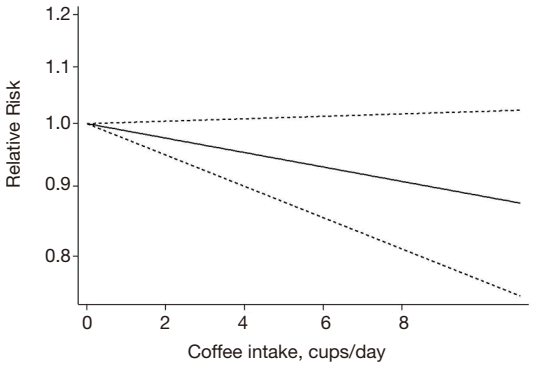

Figure 5 Relationship between coffee intake and breast cancer risk in a linear model (case-control study design).

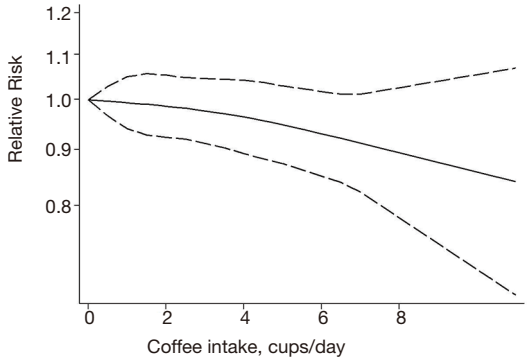

Figure 6 Relationship between coffee intake and breast cancer risk in a non-linear model (case-control study design).

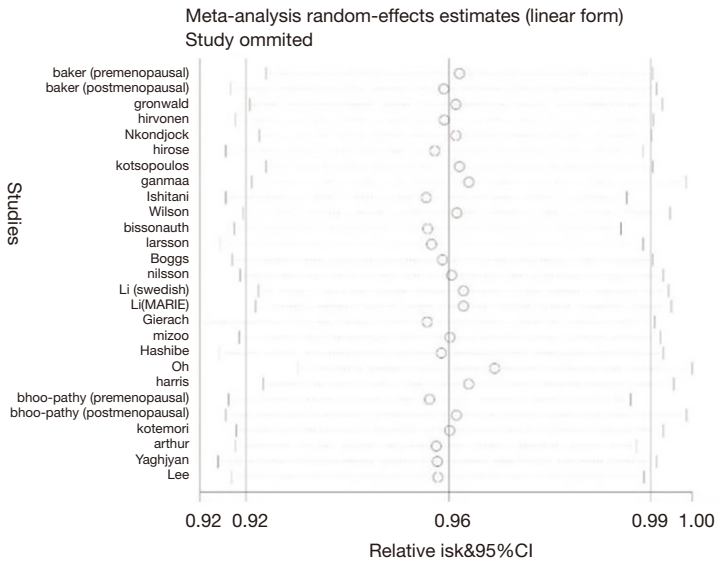

Figure 7 Sensitivity analysis (random effects model).

no significant publication bias in the analysis (Egger's test: P=0.78; Begg method: P=0.75).

Ethical approval

Ethical approval was not applicable because we did not undertake any clinical research in this study, but only collected data from available publications.

Discussion

Our meta-analysis found that coffee consumption is correlated with lower breast cancer risk (RR: 0.95; 95% CI: 0.92–0.99). This conclusion is similar to that of two previous assessments (13,14) but differs slightly from that of a third (12). Li *et al*. reported an association between coffee consumption and breast cancer risk in women with estrogen receptor-negative breast cancer (13), but this was not confirmed in our meta-analysis of up-to-date data. We found a negative correlation in postmenopausal women, which is similar to the analysis of Lafranconi *et al*. (14).

In the dose–response analysis, we found a significant linear and marginal dose–response relationship between breast cancer risk and coffee intake, in agreement with the findings of Lafranconi *et al*. for both cohort studies and case-control studies (14).

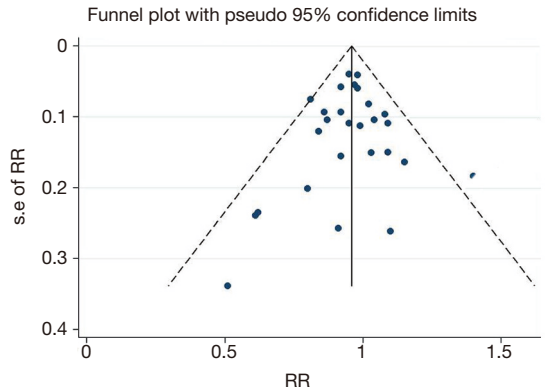

Figure 8 Funnel plot with pseudo 95% confidence limits. CI, confidence interval; RR, relative risk.

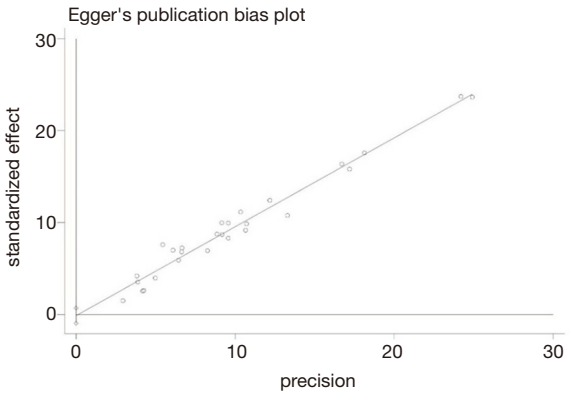

Figure 9 Egger's test of publication bias.

Coffee contains caffeine, terpenes, and polyphenols. Polyphenols and terpenes are known to exert antioxidant effects; phenols from coffee extracts have been shown to selectively kill breast cancer cells without affecting normal immune lymphocytes (47). The phenol chlorogenic acid in coffee and the onset of breast cancer have also been linked: a large cohort study found that intake of phenolic acid subtypes (such as hydroxycinnamic and hydroxybenzoic acid), triterpenoids, and monoterpenes in coffee was negatively correlated with the incidence of breast cancer (48). Phenols in coffee have been reported to augment DNA repair following damage from reactive oxygen species (49).

Regarding the relationship between coffee intake and breast cancer risk before and after menopause, our meta-analysis showed that coffee intake and breast cancer incidence were negatively correlated in postmenopausal women. The effect of menstrual status on breast cancer risk may be related to interaction between caffeine and free estradiol in premenopausal women (50-52). Sex hormone-binding globulin is a major carrier of estradiol, and high levels of sex hormone-binding globulin (which reduces free estrogen levels) in postmenopausal women have been associated with a reduction in breast cancer risk (52,53). At the same time, caffeine intake induces the activity of cytochrome P450 CYP1A enzymes. CYP1A2 is known to be involved in the pathogenesis of breast cancer and in estrogen metabolism (54,55). Some constituents of coffee are involved in the inhibition of aromatase, which promotes the generation of estrogen (50). Circulating free estrogen has been shown to be an important contributor to breast cancer (56).

Regarding geographic distribution, our meta-analysis found that in European cohorts, coffee intake and breast cancer risk were significantly negatively correlated. The analysis did not support such a relationship in Asian and North American women, contrasting with the findings of a previous meta-analysis (12). The per capita consumption of coffee has been reported to be higher in European countries than in other regions; this especially applies to northern countries such as Finland, Sweden, Iceland, Norway, Denmark, and Austria, exceeding six kilograms annually (57). We speculate that differences in intake may affect the risk of breast cancer.

We found no correlation with BMI, although obesity has been linked to breast cancer. Obesity may affect the levels of circulating free estradiol, contributing to the pathogenesis of breast cancer (56). Estrogen has been linked to DNA damage and the stimulation of blood vessels, promoting tumorigenesis (58). Coffee may reduce the risk of cancer, cardiovascular disease, and type 2 diabetes due to its antioxidative effects and influence on estrogen levels (59,60). However, the incidence of breast cancer has been linked to levels of leptin, which is involved in the JAK/STAT, MAPK, and PI3K pathways and tumor cell-related proliferation. Activation of leptin has been shown to promote the incidence, development, growth, and metastasis of breast cancer (58,61). Leptin also interacts with the signaling of insulin-like growth factor 1, which promotes breast cancer cell invasion by activating epidermal growth factor receptor (62). A cross-sectional study reported a negative correlation between coffee intake and leptin levels (63); a coffee-induced reduction in leptin levels may therefore modulate the incidence of breast cancer.

Lifestyle factors such as smoking, alcohol consumption, and use of oral contraceptives or a history of benign breast

disease did not affect the relationship between coffee intake and breast cancer risk in our meta-analysis. Although our study updates the existing evidence with more recent data, it has certain limitations. Conclusions were consistent between data from case-control and cohort studies, but there were fewer case-control studies that could be included in the dose-response analysis.

In addition, many potentially relevant factors, such as the impact of *BRCA* gene mutations, could not be analyzed because of the paucity of data.

Conclusions

Our meta-analysis found a weak negative correlation between coffee intake and breast cancer risk, especially in postmenopausal women. Geographical location may also affect the relationship; thus, this requires further study.

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Footnote

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