The role of coffee consumption in breast and ovarian cancer risk: updated meta-analyses

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ABSTRACT

Background: Coffee consumption in relation to female hormone-related cancers has been investigated but meta-analyses regarding breast and ovarian cancer include studies published up to 2012 with inconsistent results for ovarian cancer.
Methods: We conducted two updated meta-analyses of studies published up to June 2016 to quantify the association of coffee intake with breast and ovarian cancer risk with random effects models. We used the dataset developed by the International Agency for Research on Cancer Working Group for Monograph 116 meeting (May 2016). We additionally performed a PubMed search in June 2016.
Results: Summary relative risks (RRs) (95% confidence intervals (CI)) for the study-specific highest vs. lowest coffee consumption were for breast and ovarian cancer respectively: 0.97 (0.93–1.00, I^2 5.5%, 40 studies, 76,728 cases) and 1.03 (0.93–1.14, I^2 31.9%, 31 studies, 13,111 cases). For decaffeinated coffee the corresponding RRs were: 1.00 (0.93-1.08, I2 32.2%, 13 studies) and 0.83 (0.71-0.96, I2 about 0%, 9 studies). The association of coffee with ovarian cancer risk was higher among publications before (RR=1.37, 1.12–1.69) compared to after 2000 (RR=0.96, 0.86-1.06).
Conclusion: Our meta-analyses provide strong, quantitative evidence that coffee consumption is not related to breast cancer risk and appears to be unrelated to ovarian cancer risk.

Key words: coffee; breast cancer; ovarian cancer; meta-analysis; review

INTRODUCTION

Coffee is one of the most frequently consumed beverages worldwide [1]. The role of coffee consumption on the risk of female hormone-related cancers (i.e. breast, ovarian and endometrial cancers) has been investigated since the 1980's [2,3]. The accumulated evidence regarding the association of coffee intake with these cancers has been also evaluated by international research organizations (World Cancer Research Fund (WCRF)/ American Institute for Cancer Research (AICR) [4,5]; International Agency for Research on Cancer (IARC), Monographs Working Group (WG) [6, 7]). In 2016, the IARC Working Group that evaluated the carcinogenicity of coffee consumption concluded that there *was evidence suggesting lack of carcinogenicity* for cancers of the endometrium and female breast and *inadequate evidence* for ovarian cancer [7].

With respect to endometrial cancer, the up-to-date evidence is consistent with a dose-response inverse association with increased coffee consumption: this has been demonstrated in well conducted earlier meta-analyses [8], as well as, most recent ones [9].

For breast cancer, a few meta-analyses, some of which with methodological limitations, have been undertaken [10-14]. In the most-informative one [13] the meta-RR estimate, from 37 cohort and case–control studies published up to 2012, was 0.97 (95% CI 0.93–1.00) for the study-specific highest versus lowest coffee consumption, and 0.98 (95% CI 0.96–1.00) for an increment of 2 cups/day. The most-recent meta-analysis [14] included only prospective studies published up to July 2012 and found no relation overall (meta-RR: 0.99, 95%CI 0.94-1.04 for the highest versus lowest study-specific intakes).

For ovarian cancer, the information on the association with coffee intake is yet inconclusive. Two older case-control studies found an over two-fold increased risk with higher coffee intake [15, 16], and other studies reported non-significantly increased risks. Moreover, the four published meta-analyses [11, 14, 17, 18] are not fully informative. The most recent one [14], based on prospective studies published up to 2012, estimated a meta-RR of 1.04 (95% CI: 0.90-1.20) for the study-specific highest versus lowest coffee intake. The only meta-analysis, published in 2007, considering both cohort (N=4) and case-control (N=11) studies, found meta-RRs of 1.32 (95% CI 0.99, 1.77) and 1.15 (95% CI 0.89, 1.47), respectively [17].

Since the publication of the previous meta-analyses additional epidemiological data have become available. Some relevant studies [19-25] have not been considered in any of the aforementioned published meta-analyses. In this study we conducted two systematic reviews and meta-analyses to quantitatively evaluate the relation of coffee intake with breast and ovarian cancer risk using all articles published up to June 2016.

MATERIALS AND METHODS

Study selection

The flow chart for the selection procedure supplementary to IARC search is shown in Supplementary Figure 1.

This search identified 6,352 articles included in the PubMed database. On the basis of the titles and abstracts 6,187 were initially excluded whereas the remaining 165 were fully examined. From these, the following articles were not considered: 83 because they did not report information on the association of coffee consumption with breast and/or ovarian cancer; 1 study because it reported the association between total caffeine (not coffee) and breast cancer risk [26]; 3 studies considering coffee only together with tea consumption [27-29]; 3 studies on male breast cancer [30-32]; 3 studies on BRCA1 or BRCA2 mutation carriers [33-35]; 3 studies [36-38] which used the same study population as more informative studies that were included in the meta-analyses [39-41].

A total of 68 articles, the same as those considered by the Monograph 116 working group, were finally selected for the meta-analyses (overall and in specific strata) of coffee consumption in association to breast (42 articles, based on 41 studies) [3, 19-23, 25, 28, 40-73] and ovarian cancer risk (32 articles, based on 32 studies) [2, 3, 15-8, 22, 24, 25, 39, 42, 46, 57, 69, 74-91]. The sum overcomes the total because six cohort [3, 22, 25, 42, 46, 57] and one case-control [69] studies reported associations of coffee intake with both ovarian and breast cancer risk, and were included in both meta-analyses. Detailed characteristics of these studies are shown in Table 1, a and b.

Data extraction

For each study, data were extracted on study design, country, duration of follow-up (for cohort studies), enrolment period, number of subjects (cases and controls/non-cases or cohort size), age of the study population, type of coffee (e.g., total, regular/caffeinated, decaffeinated), coffee-drinking categories, estimates of RR (e.g. HR, OR etc.) and their corresponding 95% CIs, number of cases/non-cases, or, person(time)-at-risk for each coffee-drinking category (if available), and covariates adjusted for in the analysis. We selected from each study RR estimates adjusted for the largest number of confounding factors. For case–control studies providing OR estimates separately for population and hospital controls, we considered the ORs based on population controls [28, 66]. In the case-control study by Rosenberg et al. [60], we selected the ORs for breast cancer based on non-cancer controls.

Coffee was assessed in the vast majority of studies through Food Frequency Questionnaires (FFQ) enquiring

usual coffee intake over a period preceding enrolment (e.g. previous year). Most FFQs had been validated for dietary intakes, although not necessarily for coffee intake. Coffee intake was classified in cups per day, month or week in most studies.

We considered 'total coffee' when no further details on type or caffeine content were reported; when information was available we selected RRs for regular/caffeinated coffee. For the study by Schairer et al, [62], providing RRs of breast cancer for brewed and instant caffeinated coffee (but not for total/any coffee), we included in the meta-analysis the RR for brewed caffeinated coffee, as consumed by more subjects. In the Swedish Mammography Cohort [41, 74], RRs for ovarian and breast cancer for long-term coffee consumption were extracted.

Statistical analysis

Summary RRs were estimated by combining the study-specific RRs comparing the highest versus the lowest category of coffee intake using random-effects models to take into account the between-study heterogeneity [92]. Each study's log (RR) was weighted by the inverse of its variance plus the between-study variance component τ^2 computed by the moment estimator [92]. Heterogeneity among studies was evaluated with chi-square test and I^2 statistic [93, 94]. Publication bias was evaluated through funnel plots [95] and with the Egger's and Begg's tests [96].

When a study reported only the number of cases/non-cases for categories of coffee intake, we computed the crude RRs and the corresponding 95% CIs [61, 70, 86]. Moreover, when a study reported the adjusted RRs, but not the corresponding adjusted 95% CIs, we used the standard errors of the corresponding crude RRs (calculated from the distribution of cases and non-cases), to obtain the approximate CIs for the reported adjusted RRs [39, 42, 46, 65, 79, 80]. The method of Hamling et al. [97] was used to convert RR estimates when the reference category used in the analyses was not the lowest category [21, 23, 54]. In the study by Gosvig et al [24], where the RR for the coffee intake was reported only by histological type of ovarian cancer, we pooled these RRs to estimate the overall association.

We also conducted meta-analyses in strata of menopausal status for both cancer sites, in strata of body mass index (BMI) and estrogen/progesterone (ER/PR) receptor status for breast cancer, and in strata of histological type and severity of the neoplasm for ovarian cancer. Details on handling specific studies in the stratified analyses can be found in Supplementary Table 1.

Sensitivity analyses were carried out by omitting one study at a time from the analyses and assessing its effect on the overall summary RRs as estimated before and after the exclusion of each study.

A cumulative meta-analysis over year of publication was also performed for ovarian cancer.

The statistical analyses were conducted using Stata statistical software version 14.1 (StataCorp LP).

RESULTS

Breast cancer
Individual studies

In Table 1a the main characteristics of the 24 cohort and 18 case-control studies (including a total of 76,728 breast cancer cases) considering a quantitative relation between coffee intake and breast cancer risk are shown.

All studies were included in the overall meta-analysis except the studies by Michels et al [48] and Bhoo Pathy et al [54], as the studies of Larsson et al [41] and of Bhoo Pathy et al [21], respectively, refer to/included the same cohorts, but were more informative. The former studies [48, 54] were, however, used in stratified analyses by BMI. Out of the indicated 22 cohort and 18 case-control studies, 15 were conducted in North America, 18 in Europe and 7 in Asia.

Figure 1 shows the overall RRs of breast cancer for the study-specific highest versus lowest coffee drinking categories, overall and by study design. The studies by Mannisto et al [66], Baker et al, [68], and Bhoo Pathy et al [21] were included twice in the meta-analysis as they reported RRs separately for pre- and post-menopausal women. Moreover, the article by Li et al [73] reported RRs from two case-control data sets, undertaken in Sweden and Germany (MARIE Study) and was also included twice in the meta-analysis.

All cohort and most case-control studies reported null associations. Only one small case-control study [71] reported a significantly increased risk (RR: 1.40, 95% CI, 1.09-2.24). Two case-control studies [19, 28] reported significant inverse associations (RR: 0.60, 95%CI 0.20-0.90, and RR: 0.71, 95%CI 0.51-0.98, respectively), while one additional study [68] reported an inverse association in pre-menopausal (RR: 0.62, 95%CI 0.39-0.98) but not in post-menopausal women (RR: 0.99, 95%CI 0.79-1.23)

Summary estimate

The summary RR of breast cancer risk for the highest versus lowest coffee consumption was indicative of a null association: overall: 0.97 (95% CI 0.93-1.00); cohort: 0.98 (95% CI 0.94-1.02); case-control: 0.93 (95% CI 0.86-1.01). No heterogeneity was found overall (I^2 5.5

TABLE 1A. Main characteristics of the studies on breast cancer (BC) and ovarian cancer (OC) and coffee consumption included in the meta-analyses - Breast cancer

Study No	Study Reference	Location	Enrollment/ follow-up	Cohort size (BC Cases) / Cases/ controls	Cohort/ Program	Coffee categories (highest vs lowest)	Exposed cases[3]	Covariates controlled for in the Relative Risk estimate
	Cohort studies							
1	Snowdon and Phillips (1984)1[3]	USA	1960-1980/21 years	23,912 (men & women) (176)	White, Seventh-day Adventists	Cups/day >2/<1	26/131	Age, meat consumption, smoking
2	Jacobsen et al, (1986) [42]	Norway	1967-69/11,5 years	2,891 (32)	Two Norwegian cohorts	Cups/day >7/<2	3/12	Age, sex and residence
3	Vatten et al. (1990) [43]	Norway	1974-1977 /12 years	14,593 (152)	National Health Screening Service for CVD	Cups/day >7/<2	21/27	Age
4	Hoyer & Engholm (1992) [44]	Denmark	1964-1986 /4-26 years	5,207(51)	Glostrup Population Studies	Cups/day >7/<2	NR	Not clear. Possibly for social class, age at menarche, menopause status, number of full-term pregnancies, height, weight, BMI, alcohol and smoking,
5	Folsom et al. (1993) [45]	USA	1986/1990	34,388 (580)	Iowa Women's Health Study	Cups ≥4 per day/ never-<1/month	106/183	Age, waist/hip ratio, number of livebirths, age at first livebirth, age at menarche, family history of BC, as well as interactions of family history with waist/hip ratio, and number of livebirths
6	Stensvold and Jacobsen (1994) [46]	Norway	1977-1982/10 years	21,238 (211)	Cardiovascular screening program	Cups/day ≥7/≤ 2	43/22	Age, cigarettes per day and county of residence
7	Key at al, (1999) [47]	Japan	1969-1970; 1979-1980/ up to 1993	34,759 (427)	Radiation Effects Research Foundation's Life Span Study	Times/week >5/<1	122/151	Attained age, calendar period, city of residence, age at the time of the bombing and radiation dose
8	Michels et al. (2002)2[48]	Sweden	1987-1990 /9.5 years	59,036 (1271)	Swedish Mammography Screening Cohort	Cups/day ≥4/≤1	214/76	Age, family history of BC, height, BMI, education, parity, age at first birth, alcohol consumption and total caloric intake
9	Suzuki et al. (2004) [49]	Japan	Cohort 1: 1984/9 years Cohort 2: 1990/7 years	Cohort 1: 14,409 (103) Cohort 2: 20,595 (119)	Population-based prospective cohort study	Cups/day ≥1/never	NR	Age, types of health insurance, age at menarche, menopausal status, age at first birth, parity, mother's history of BC, smoking, alcohol drinking and BMI
10	Hirvonen et al. (2006) [50]	France	1994/6.6 years	4396 (95)	Participants in the double blind clinical trial Supplementation en Vitamines et Mineraux Antioxydants Study (SU. VI.MAX)	ml/day: tertiles >253/≤111	33/30	Age, smoking, menopausal status, oral contraception use, family history of BC, number of children

BMI: body mass index; CVD: Cardiovascular diseases; HRT: hormone replacement therapy; H: hospital controls; P: population controls; 1: Breast cancer mortality; 2: Used only in stratified analysis; 3: Breast cancer cases in coffee categories contrasted in the RR estimate; 4 : This study was described as nested case–control in the original publication. It was analysed as case-control, however, since the nested case-control design was not clearly described in the respective paper.

%); however, the heterogeneity was higher among case-control studies (I^2 34.2%) and null among cohort studies (I2 approximately 0%). When the meta-analysis was confined to the 13 studies considering as the highest category of coffee consumption women drinking at least 4 cups/day (and with any type of reference category), the summary RR was of 0.94 (95% CI 0.86-1.03, p-heterogeneity 0.219, I^2 21.6%). Additionally, among the 14 studies considering as the highest category of coffee consumption women drinking at least 3 cups/day (with reference category non-coffee drinkers), the summary RR was 0.98 (95% CI 0.93-1.03, p-heterogeneity 0.305, I^2 13.2%).

Caffeinated and decaffeinated coffee intake

Supplementary Figure 2 shows the forest plot of RRs of breast cancer corresponding to the highest versus lowest decaffeinated coffee intakes from the 8 case-control and 5 cohort studies reporting such

TABLE 1A (CONTINUED). Main characteristics of the studies on breast cancer (BC) and ovarian cancer (OC) and coffee consumption included in the meta-analyses - Breast cancer

Study No	Study Reference	Location	Enrollment/ follow-up	Cohort size (BC Cases) / Cases/ controls	Cohort/ Program	Coffee categories (highest vs lowest)	Exposed cases[3]	Covariates controlled for in the Relative Risk estimate
	Cohort studies							
11	Ganmaa et al. (2008) [51]	USA	1976/ 1980-2002	85,987 (5,272)	Nurses Health Study (NHS)	Cups ≥4 per day/<1/ month	637/837	Age, smoking status, BMI, physical activity, height, history of benign breast disease, family history of BC, weight change since age 18, age at menarche, parity, age at first birth, alcohol intake, total energy intake, age at menopause and postmenopausal hormone use
12	Ishitani et al. (2008) [52]	USA	1992 /10 years	38,432 (1188)	US health professionals: selection of participants in a randomised study	Cups ≥4 per day/ almost never	191/274	Age and randomized treatment, as well as, for: alcohol consumption, BMI, family history of BC, history of hysterectomy, bilateral oophorectomy, smoking status, history of benign breast disease, age at menarche, parity, age at first birth, physical activity, total energy intake, multivitamin use, age at menopause, menopausal status, and postmenopausal hormone use
13	Larsson et al. (2009) [41]	Sweden	1987-1990 / up to 2009	61,433 (2,952)	Swedish Mammography Cohort	Cups/day >4 vs <1	492/251	Age, education, BMI, height, parity, age at first birth, age at menarche, age at menopause, use of oral contraceptives, use of postmenopausal hormones, family history of BC, and intakes of alcohol, tea and total energy
14	Wilson et al. (2009) [53]	USA	1991/14 years	90,628 (1,179)	Nurses Health Study II (NHS II)	Quintiles of servings/day 5th/1st	258/270	Age, calendar year, BMI, height, oral contraceptive use, parity and age at first birth, age at menarche, family history of BC, history of benign breast disease, smoking, physical activity, animal fat, glycemic load, alcohol intake, and total energy intake

BMI: body mass index; CVD: Cardiovascular diseases; HRT: hormone replacement therapy; H: hospital controls; P: population controls; 1: Breast cancer mortality; 2: Used only in stratified analysis; 3: Breast cancer cases in coffee categories contrasted in the RR estimate; 4 : This study was described as nested case–control in the original publication. It was analysed as case-control, however, since the nested case-control design was not clearly described in the respective paper.

information. The association was direct in one large case-control study [64] (RR: 1.20, 95%CI 1.03-1.39) and inverse in another one [40] (RR: 0.84, 95% CI 0.72-0.98). The RRs from the remaining studies were not significantly different from unity. The summary RR was 1.00 (95% CI 0.93 to 1.08), with overall low between-study heterogeneity (p-heterogeneity 0.550, I2 32.2%).

Analysis of regular/caffeinated coffee intake indicated similar findings to the overall meta-analysis and was based on 11 studies with available information. The overall RR for the highest versus lowest reported coffee intake was 0.93 (95% CI 0.89, 0.97) (data not shown).

Subgroup analysis

Summary RRs (95% CI) of breast cancer risk for the highest versus the lowest coffee consumption in

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Study No	Study Reference	Location	Enrollment/ follow-up	Cohort size (BC Cases) / Cases/ controls	Cohort/ Program	Coffee categories (highest vs lowest)	Exposed cases[3]	Covariates controlled for in the Relative Risk estimate
	Cohort studies							
15	Bhoo-Pathy et al. (2010)2[54]	Netherlands	1993–1997/9.6 years	27,323 (681)	European Investigation into Cancer and nutrition (EPIC) -Netherlands	Cups/day >5/>0-1	151/110	Age at recruitment, smoking status, educational status, BMI, alcohol and energy intake, fat and fiber intake, tea intake, physical activity level, ever prior use of oral contraceptives, presence of hypercholesterolemia, cohort, family history of BC, age at menarche, and parity
16	Boggs et al. (2010) [55]	USA	1995/ 12 years	52,062 (1268)	Black Women's Health Study	Cups/day >4/ never-<1/mo	49/592	Energy intake, age at menarche, BMI at age 18, family history of BC, education, geographic region, parity, age at first birth, oral contraceptive use, menopausal status, age at menopause, menopausal hormone use, vigorous activity, smoking status, and alcohol, tea and decaffeinated coffee intakes
17	Iwasaki et al. (2010) [56]	Japan	1990 (Cohort I); 1993 (Cohort II) /2006	53,793 (581)	Japan Public Health Center-based Prospective Study	Cups ≥3 per day/<1 per week	63/161	Age, area, age at menarche, menopausal status at baseline, age at menopause for postmenopausal women, number of births, age at first birth, height, BMI, alcohol intake among regular drinkers, smoking, leisure time physical activity, exogenous hormone use, family history of breast cancer, green tea, oolong tea, and black tea intakes
18	Nilsson et al. (2010) [57]	Sweden	1992-2007 /2007	32,178 (587)	Vasterbotten Intervention Project	Occasions/ day ≥4/<1	163/58	Sex, age, BMI, smoking, education, and recreational physical activity
19	Fagherazzi et al. (2011) [58]	France	1990/2005	67,703 (2,868)	Teachers, insured by the national health insurance system	Cups/day >3/non-consumer	834/410	Age, baseline variables (total energy intake, ever use of oral contraceptives, age at menarche, age at menopause, number of children, age at first pregnancy, history of BC in the family and years of schooling) and time-dependent variables (current use of postmenopausal hormone therapy (for postmenopausal women only), personal history of benign breast disease, menopausal status and BMI

BMI: body mass index; CVD: Cardiovascular diseases; HRT: hormone replacement therapy; H: hospital controls; P: population controls; 1: Breast cancer mortality; 2: Used only in stratified analysis; 3: Breast cancer cases in coffee categories contrasted in the RR estimate; 4 : This study was described as nested case–control in the original publication. It was analysed as case-control, however, since the nested case-control design was not clearly described in the respective paper.

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Study No	Study Reference	Location	Enrollment/ follow-up	Cohort size (BC Cases) / Cases/ controls	Cohort/ Program	Coffee categories (highest vs lowest)	Exposed cases[3]	Covariates controlled for in the Relative Risk estimate
	Cohort studies							
20	Gierach et al. (2012) [59]	USA	1995–1996 /2006	198,404 (9,915)	National Institutes of Health-AARP Diet and Health Study	Cups/day >4/never	1217/1138	Age at entry, race/ethnicity, education, BMI, smoking status and dose, alcohol, proportion of total energy from fat, age at first live birth, menopausal hormone therapy (HT) use, history of breast biopsy, and family history of breast cancer in a first degree relative
21	Bhoo-Pathy et al. (2015) [21]	Europe	1992-2000 /2010	335,060 (10,198)	European Investigation into Cancer and nutrition (EPIC)	ml/day high/no intake	252/81 (pre-menopausal) 1860/732 (post-menopausal)	Age at menarche, ever use of oral contraceptives, age at first delivery, ever breastfeeding, smoking status, education, physical activity, alcohol, height, weight, energy intake from fat and non-fat sources, total saturated fat and fiber intakes, tea intake, as well as, ever-use of postmenopausal hormones
22	Hashibe et al. (2015) [22]	USA	1992, 2001 / 2011	50563 (1703)	Prostate, Lung, Colorectal, and Ovarian cancer screening trial (PLCO)	Cups/day ≥2/<1 1cup increment	828/599	Age, sex, race, education, cigarette pack-years, and alcohol drinking frequency
23	Oh et al. (2015) [23]	Sweden	1991-1992 /2012	42,099 (1395)	Women's Lifestyle and Health	Cups/day >5/0 1cup/day increment	421/99	Age, BMI, duration of breastfeeding, and alcohol consumption, as well as, smoking status, education, and physical activity (in sensitivity analyses)
24	Lukic et al. (2016) [25]	Norway	1991-1992, 1996-1997, 2003,2004 /1996-2013	91,767 (3,277)	The Norwegian Women and Cancer	Cups/day >7 vs ≤1	182/626	Menopausal status, smoking status, education, BMI, physical activity level, alcohol consumption, number of children age at first birth, use of hormone replacement therapy, and maternal history of breast cancer – repeated measures for these factors, as well as, for coffee intake were also taken considered

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strata of selected covariates are shown in Table 2. No significant heterogeneity was found by caffeine content, geographic area, menopausal status, BMI and, among case-controls studies, by type of controls. ER/PR breast cancer type was reported in 6 cohort studies [21, 23, 41, 55, 58, 59] for all or for a subgroup of participants only (13,346 cases). There was no evidence of heterogeneity across strata of ER/PR. Within ER/PR strata, between-study heterogeneity was not statistically significant and medium to low, with the exception of RRs among the ER+/PR- subgroup (4 studies) for which heterogeneity was 70.4%.

Sensitivity analysis and publication bias

In sensitivity analysis, the summary RR of breast cancer in association to coffee intake (highest versus

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	Cohort studies							
1	Lubin et al. (1985) [28]	Israel	1975 -1979	807/807 P		Cups/day >4/0	155/141	Age, country of origin, length of residence in Israel.
2	Rosenberg et al. (1985) [60]	USA	1975-1982	2,651 /1501 H (non cancer controls)		Cups/day >5/0	413/493	Age, race, religion, cigarette smoking, age at menarche, age at first pregnancy, parity, type of menopause, age at menopause, history of fibrocystic breast disease, family history of BC (in the mother or sister(s)), BMI, years of education, tea and alcohol consumption, location of the hospital, year of interview, and number of previous non-obstetric hospitalizations
3	Katsouyanni et al. (1986) [61]	Greece	1983–1984	120 /120 H		Tertiles of frequency of use 3rd/1st	24/29	No adjustment
4	Schairer et al. (1987) [62]	USA	1977-1980	1510 /1882 P	Breast Cancer Detection Demonstration Project (screening project)	Cups/day (brewed coffee) >5/0	194/171	No adjustment, but matching for age, center, screening program entry and duration
5	Ewertz and Gill (1990) [63]	Denmark	1983-1984	1474 /1322 P		Cups/day >10/<3	82/358	Age at diagnosis and place of residence
6	McLaughlin et al. (1992) [64]	USA	1982-1984	1617 /1617 P		Drinkers/non drinkers	1463/154	Age, county of residence, race, menstrual status, age at first live birth, history of benine breast disease, family history of breast cancer and alcohol intake
7	Levi et al. (1993) [65]	Switzerland	1992	107 /318 H		Tertiles of frequency of use 3rd/1st	33/32	Age
8	Tavani et al. (1998) [40]	Italy	1983-1991 and 1991-1994	5,984 /5,504 H		Cups/day >4/0	784/812	Study/centre, age, education, BMI, smoking status, total alcohol intake, age at menarche and menopause, parity and age at first birth, use of oral contraceptives, use of HRT, history of benign breast disease and family history of breast cancer.
9	Mannisto et al. (1999) [66]	Finland	1990-1995	310/454 P		Quintiles of g/day >488/<120 (pre-menopausal) >488/<240 (post-menopausal)	NR	Age, area (rural/urban), age at menarche, age at first full-term pregnancy, use of oral contraceptives, use of estrogen replacement therapy, first-degree family history of breast cancer, history of benign breast disease, level of education, current alcohol intake, smoking habits, leisure activity and waist-to-hip ratio.

BMI: body mass index; CVD: Cardiovascular diseases; HRT: hormone replacement therapy; H: hospital controls; P: population controls; 1: Breast cancer mortality; 2: Used only in stratified analysis; 3: Breast cancer cases in coffee categories contrasted in the RR estimate; 4 : This study was described as nested case–control in the original publication. It was analysed as case-control, however, since the nested case-control design was not clearly described in the respective paper.

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Study No	Study Reference	Location	Enrollment/ follow-up	Cohort size (BC Cases) / Cases/ controls	Cohort/ Program	Coffee categories (highest vs lowest)	Exposed cases[3]	Covariates controlled for in the Relative Risk estimate
	Cohort studies							
10	Wu et al. (2003) [67]	USA (Asian population)	1995 -1998	501 /594 P	Los Angeles County Cancer Surveillance Program	ml/day >240/0	152/135	Education, age at menarche, pregnancy, current BMI, total caloric intake, menopausal status and use of menopausal hormones intake of soy, dark green vegetables smoking history, alcohol intake, physical activity, and family history of BC
11	Baker et al. (2006) [68]	USA	1982-1988	1932 /1895 H		Cups/day >4/<1	57/136 (pre-menopausal) 261/462 (post-menopausal)	Age, residence, and age at birth of first child
12	Hirose et al. (2007) [69]	Japan	1990-2000	2122 /12,425 H	Hospital-based Epidemiological Research Program at Aichi Cancer Center (HERPACC)	Cups/day >3/0	254/448	Age, year, motivation for consultation, parity, age at first delivery, smoking, drinking, exercise and BMI, as well as for a number of dietary variables
13	Zhang et al, (2007) [70]	China	2004 - 2005	1009 /1009 H		Yes/no	98/120	No adjustment
14	Bissonauth et al. (2009)4 [71]	Canada	2004-2006	280 /280 P		Cups/day >8/≤2	88/102	Age, education, physical activity, smoking, coffee consumption and total energy intake
15	Rabstein et al. (2010) [72]	Germany	2000-2004	1020 /1047 P	Gene-ENvironment Interaction and breast CAncer (GENICA)	Cups/day ≥4/0	379/145	Age, breast cancer in mother or sister, HRT, number of mammograms, physical activity, lifetime breastfeeding
16	Li et al. (2011) [73]	Sweden Germany	1993-1995 2002-2005	2818 /3111 P 2651 /5395 P	Swedish Study Mamma Carcinoma Risk factor Investigation (MARIE) Study	Cups/day >5/≤1	328/298 157/287	Age at enrolment, HRT, smoking, education and daily alcohol consumption
17	Lowcock et al. (2013) [19]	Canada	2002, 2003	3,062 /3,427 P		Cups/day >5/never	71/540	age, smoking status, ethnicity and level of strenuous physical activity as a teenager
18	Mizoo et al. (2013) [20]	Japan	2010 -2011	472 /464 P		Times/week ≥4/<1	45/132	Age

BMI: body mass index; CVD: Cardiovascular diseases; HRT: hormone replacement therapy; H: hospital controls; P: population controls; 1: Breast cancer mortality; 2: Used only in stratified analysis; 3: Breast cancer cases in coffee categories contrasted in the RR estimate; 4 : This study was described as nested case–control in the original publication. It was analysed as case-control, however, since the nested case-control design was not clearly described in the respective paper.

lowest intake) did not change appreciably when each study was excluded in turn and the RR was estimated from the remaining studies (RRs range: 0.96 to 0.97, not significant in all analyses). The funnel plot of individual RRs for breast cancer studies is shown in Supplementary Figure 3. There was no indication for publication bias for studies investigating the association of coffee intake with breast cancer risk (p-values of Egger's and Begg's test: 0.877 and 0.753, respectively).

Ovarian cancer

Individual studies

Table 1b shows the main characteristics of the 13

TABLE 1B. Main characteristics of the studies on breast cancer (BC) and ovarian cancer (OC) and coffee consumption included in the meta-analyses - Ovarian cancer

Study No	Study reference	Location	Enrollment/ follow-up	Cohort size (OC cases) / Cases/ controls	Cohort/ Program	Coffee categories (highest vs lowest)	Exposed cases[3]	Covariates controlled for in the Relative Risk estimate
	Cohort studies							
1	Snowdon and Phillips (1984)1[3]	USA	1960-1980/21 years	23,912 (men and women) (51)	Seventh-day Adventists	Cups/day >2/<1	10/35	Age, meat consumption, smoking
2	Jacobsen et a (1986) [42]	Norway	1967-69/11,5 years	2,891 (12)	Two Norwegian cohorts	Cups/day >7/<2	1/5	Age and residence
3	Stensvold and Jacobsen (1994) [46]	Norway	1977-1982/10 years	21,238 (93)	Cardiovascular screening program	Cups/day ≥7/≤ 2	18/5	Age, cigarettes per day and county of residence
4	Larsson and Wolk (2005) [74]	Sweden	1987-1990/ 15,1 years	61,057 (301)	Swedish Mammography Screening Cohort	Cups/day ≥4/<1	49/24	Age, BMI, education, parity, use of oral contraceptives, total energy intake, fruits, intake of vegetables, milk, tea
5	Silvera et al. (2007) [75]	Canada	1980-1985/ 16,4 years	48,776 (264)	Canadian Cancer Breast Screening Study (NBSS)	Cups/day ≥4/0	41/34	Age, smoking, alcohol consumption, education, BMI, parity, physical activity, menopause, use of oral contraceptives, total energy intake, lactose, study center, randomization group
6	Steevens et al. (2007) [17]	The Netherlands	1986-1999/ 13,3 years	2,083 (280)	Netherlands Cohort Study	Cups/day ≥5/<1	59/15	Age, use of oral contraceptives, parity, smoking, tea
7	Lueth et al. (2008) [76]	USA	1986/ 16 years	29,060 (266)2	Iowa Women's Health Study (IWH)	Cups/day ≥5/0	40/24	Age, smoking, BMI, age at menopause, parity, use of oral contraceptives, education, physical activity, total energy intake
8	Tworoger et al. (2008) [77]	USA	1976-1980/ 24 years	80,253 (507)	Nurses' Health Study (NHS)	Cups/day (Caffeinated coffee) ≥3/0	97/78	Age, parity, use of oral contraceptives, HRT, tubal ligation, smoking, BMI
9	Kotsopoulos et al. (2009) [78]	USA	1976-2004	234 cases/691 controls (nested case-control study)	Nurses' Health Study (NHS); Nurses' Health Study II (NHS II)	Cups/day ≥2.5/<2/5	66/151	Age, parity, use of oral contraceptives, HRT, tubal ligation, smoking, BMI, family history of breast/ ovarian cancer
10	Nilsson et al. (2010) [57]	Sweden	1985-1994/ 6 years	32,178 (71)	Vasterbotten Intervention Project	Occasions/ day ≥4/<1	25/5	Age, BMI, education, physical activity, smoking
11	Braem et al. (2012) [18]	Europe	1992-2000/11.7 years	330,849 (1244)	European Prospective Investigation into Cancer and nutrition (EPIC)	ml/day 5th quintile/ no-consumers	189/84	Age, parity, use of oral contraceptives, BMI, smoking, alcohol consumption, total energy intake, breastfeeding, menopause, height, education
12	Hashibe et al. (2015) [22]	USA	1992-2001/ 10-13 years	50,563 (162)	Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO)	Cups/day ≥2/<1 1 cup/day increment	82/50	Age, race, education, smoking, alcohol consumption
13	Lukic et al. (2016) [25]	Norway	1991-2004/1996-2013	91,797 (446)	Norwegian Women and Cancer Study	Cups/day >7/<1	NR	Age, menopause, smoking, education, parity, use of oral contraceptives, HRT, maternal history of breast cancer

BMI: body mass index; CVD: Cardiovascular diseases; HRT: hormone replacement therapy; H: hospital controls; P: population controls; 1: Ovarian cancer mortality; 2: Used only in stratified analysis by histological type of ovarian cancer 3:Contrasted in the RR estimation

TABLE 1B (CONTINUED). Main characteristics of the studies on breast cancer (BC) and ovarian cancer (OC) and coffee consumption included in the meta-analyses - Ovarian cancer

Study No	Study reference	Location	Enrollment/ follow-up	Cohort size (OC cases) / Cases/ controls	Cohort/ Program	Coffee categories (highest vs lowest)	Exposed cases[3]	Covariates controlled for in the Relative Risk estimate
	Case Control studies							
1	Hartge et al. (1982) [2]	USA	NR	158 /187H		Cups/day: ≥4/0	38/39	Age, parity, smoking
2	Byers et al. (1983) [79]	USA	1957-1965	274 /1034 H		Cups/day: ≥3/0	126/52	Age, parity, smoking
3	Cramer et al. (1984) [80]	USA	1978-1981	215 /215 P		Cups/day: ≥5/<0	36/28	Age, parity
4	Tzonou et al. (1984) [39]	Greece	1980-1981	150 /250 H		Cups/day ≥3.5/0	11/26	Age, parity, age at menopause, smoking, alcohol consumption, estrogen use
5	La Vecchia et al (1984) [15]	Italy	1979-1983	247 /494 H		Cups/day ≥4/0	39/74	Education, age, parity, age at first birth, use of oral contraceptives, age at menopause, BMI, smoking, alcohol consumption
6	Miller et al. (1987) [81]	USA	1976-1983	290 /580 H (non-cancer controls)		Cups/day ≥5/0	36/92	Age, race, religion, smoking, alcohol consumption, use of oral contraceptives, conjugated estrogen use, BMI, age at menarche, age at first pregnancy, age at menopause, type of menopause, education, geographical location of hospital, year of interview, number of non obstetric hospital admissions
7	Mori et al. (1988) [82]	Japan	1980-1981, 1985-1986	110 /110 P		Daily / non-daily consumption	46/64	Age, year of interview, smoking, BMI, alcohol consumption, milk, meat, fish
8	Whittemore et al. (1988) [16]	USA	1983-1985	280 /259 P		Cups/day17 ≥4/0	54/11	Age, race, year of interview, hospital, smoking
9	Polychronopoulou et al. (1993) [83]	Greece	1989-1991	189/200 P		Cups/day >2/never	93/18	Age
10	Kuper et al. (2000)2 [84]	USA	1992-1997	549 /516 P	New England Case-Control Study (NECC)	Cups/day >4/never	61/128	Age, center, parity, BMI, oral contraceptives, , family history of breast/ovarian/ prostate cancer, tubal ligation, education, alcohol consumption, smoking, marital status
11	Tavani et al. (2001) [85]	Italy	1992-1999	1031 /2411 H		Cups/day >4/<1	155/188	Age, study center, year of interview, education, parity, age at menopause, oral contraceptives use, BMI, total energy intake, family history of ovarian/ breast cancer

BMI: body mass index; CVD: Cardiovascular diseases; HRT: hormone replacement therapy; H: hospital controls; P: population controls; 1: Ovarian cancer mortality; 2: Used only in stratified analysis by histological type of ovarian cancer 3:Contrasted in the RR estimation

TABLE 1B (CONTINUED). Main characteristics of the studies on breast cancer (BC) and ovarian cancer (OC) and coffee consumption included in the meta-analyses - Ovarian cancer

Study No	Study reference	Location	Enrollment/ follow-up	Cohort size (OC cases) / Cases/ controls	Cohort/ Program	Coffee categories (highest vs lowest)	Exposed cases[3]	Covariates controlled for in the Relative Risk estimate
13	Goodman et al. (2003) [87]	Hawaii	1993-1999	164 /194 P		Cups/day >1/non-drinkers	64/32	Age, race, use of oral contraceptives, tubal ligation
14	Jordan et al. (2004) [88]	Australia	1990-1993	696 /786 P		Cups/day >4/non-drinkers	86/127	Age, BMI, use of oral contraceptives, parity, smoking, alcohol consumption, education, energy intake
15	Riman et al. (2004) [89]	Sweden	1993-1995	655 /3899 P		Cups/day >6/non-drinkers	61/33	Age, parity, BMI, age at menopause, use of oral contraceptives, HRT
16	Baker et al. (2007) [90]	USA	1982-1998	414 /868 H		Cups/day >4/non-drinkers	66/139	Age, residence, year of interview
17	Hirose et al. (2007) [69]	Japan	1990-2000	166 /3224 H		Cups/day: >3/non-drinkers	20/35	Age, year of interview, motivation of consultation, parity, age at first birth, smoking, alcohol consumption, physical activity, BMI, various dietary items
18	Song et al. (2008) [91]	USA	2002-2005	781 /1263 P		Cups/day: >3/non-drinkers	123/216	Age, county, year of diagnosis, race, parity, duration of use of oral contraceptives, BMI, smoking, tubal ligation/ hysterectomy, family history of breast/ovarian cancer
	Kotsopoulos et al. (2009) [78]	USA	1992-1997 and 1998-2003	1120/1160 P	New England Case-Control Study (NECC)	Cups/day: >2.5/<2.5	400/645	Age, parity, use of oral contraceptives, HRT, tubal ligation, family history of breast/ovarian cancer, BMI, smoking
19	Gosvig et al. (2015) [24]	Denmark	1995-1999	382 /911 P		Cups/day: >4/none	109/27	Age, parity, use of oral contraceptives

BMI: body mass index; CVD: Cardiovascular diseases; HRT: hormone replacement therapy; H: hospital controls; P: population controls; 1: Ovarian cancer mortality; 2: Used only in stratified analysis by histological type of ovarian cancer 3:Contrasted in the RR estimation

cohort and 19 case-control studies (including a total of 13,111 ovarian cancer cases) considering a quantitative relation between coffee intake and ovarian cancer risk.

All studies were included in the overall meta-analysis except for the study by Kuper et al [84], as the study of Kotsopoulos et al [78] included the same case-control dataset, but was more informative. The study by Kuper et al [84] was, however, included in stratified analyses by BMI.

From the indicated 13 cohort and 18 case-control studies included in the overall meta-analysis 14 were conducted in North America, 13 in Europe, 3 in Asia and 1 in Australia.

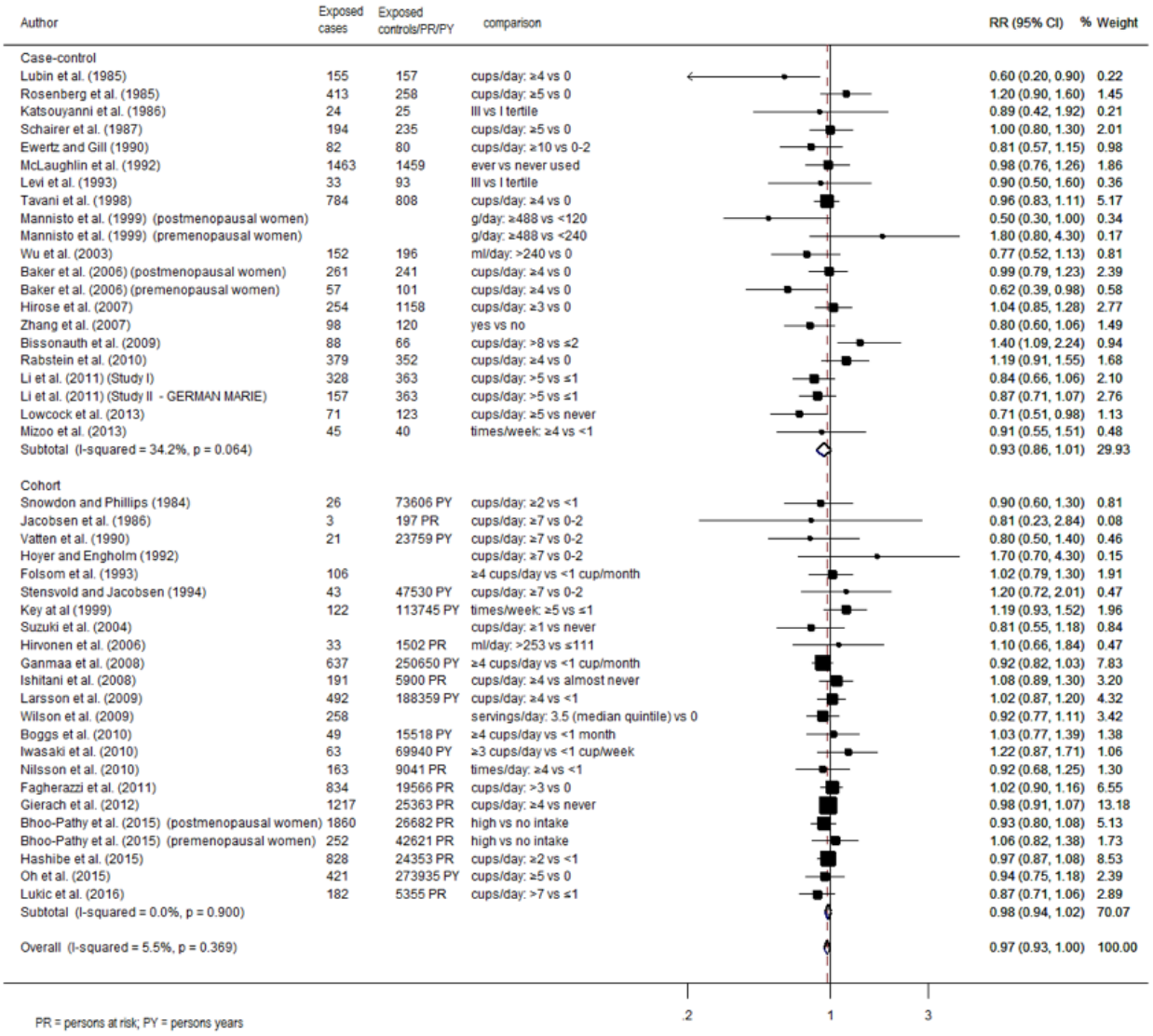
The RRs for ovarian cancer comparing the highest with the lowest coffee intake are shown in Figure 2. The study by Kotsopoulos et al [78] was included twice in the meta-analysis – one as a cohort and one as a case-control study, because it included the pooled estimates from the Nurses' Health Study and the Nurses' Health Study II (cohort studies) and the estimate of the NEEC study (a case-control study).

Cohort studies revealed no relation. Among case-control studies, one [15] reported a significantly increased risk (RR: 2.20, 95% CI 1.20-3.90), and two studies [86, 88] reported inverse associations (RR: 0.66, 95% CI 0.47-0.93, and, RR: 0.62, 95% CI 0.41-0.95, respectively).

Summary estimate

The summary RR for all studies was 1.03 (95% CI 0.93–1.14); 1.03 (95% CI 0.89 to 1.19) among case-control, and 1.03 (95% CI 0.90, 1.18) among

FIGURE 1. Relative risks (RRs) and 95% confidence intervals (CI) of breast cancer for the highest versus the lowest coffee drinking category from case-control and cohort studies, and from all the studies combined. The combined RRs and 95% CI were calculated using the random-effects models.



cohort studies. Overall between-study heterogeneity was moderate (I2 31.9 %), higher among case-control (I2 44.3%) than among cohort (I2 8.9%) studies. When the analysis included only the 13 studies considering as the highest category of coffee consumption women drinking at least 4 cups/day (with any type of reference category), the summary RR was 0.99 (95% CI 0.83-1.17, p-heterogeneity 0.155, I2=28.8%). In addition, when only the 15 studies having as highest category of consumption at least 3cups/day (with reference category non-coffee drinkers) were analyzed, the summary RR was of 1.11 (95% CI 0.92-1.34, p-heterogeneity 0.025, I2 46.5%).

Caffeinated/decaffeinated coffee intake

Five case-control and 4 cohort studies reported associations between decaffeinated coffee intake and ovarian cancer risk. Supplementary Figure 4 shows the forest plot of the RRs for the highest versus the lowest decaffeinated coffee intakes. The RR tended to be below unity in all studies, with significant inverse associations in two studies [85, 90] (RR: 0.64, 95%CI 0.42-0.96, and RR: 0.71, 95%CI 0.51-0.9, respectively). Only one study [87] had a RR above unity (RR=1.10, non-statistically significant). The overall association was inverse and significant (RR 0.83 (95% CI 0.71 to 0.96), I2 approximately 0). Information on caffeinated coffee was available in 6 studies. The overall RR for the association

TABLE 2. Summary relative risks (RRs) and 95% confidence intervals (CI) of breast cancer for the highest versus the lowest coffee drinking category in strata of selected covariates.

	N studies	RR (95% CI)	P-heterogeneity among studies	I^2
Type of coffee				
Caffeinated	11	0.93 (0.89-0.97)	0.295	16.6%
Decaffeinated	13	1.00 (0.93-1.08)	0.550	0.0%
P-heterogeneity[a]=0.099				
Geographic area				
North America	15	0.97 (0.92-1.02)	0.285	14.7%
Asiab	7	0.98 (0.85-1.14)	0.177	32.9%
Europe	18	0.96 (0.91-1.01)	0.552	0%
Northern Europec	12	0.94 (0.85-1.02)	0.241	19.5%
Southern Europec	5	0.99 (0.91-1.09)	0.949	0%
P-heterogeneity[a,d]=0.943				
Menopausal statuse				
Pre-menopause	13	0.99 (0.90-1.08)	0.395	5.1%
Post-menopause	16	0.94 (0.89-1.00)	0.152	26.4%
P-heterogeneity[a]=0.376				
Body mass indexf				
Normo weight	6	0.94 (0.85-1.04)	0.502	0.0%
Overweight	6	1.00 (0.89-1.13)	0.452	0.0%
P-heterogeneity[a]=0.438				
Receptor status				
ER+/PR+	6	1.00 (0.92-1.08)	0.691	0.0%
ER+/PR-	4	0.85 (0.61-1.19)	0.018	70.4%
ER-/PR+	3	0.69 (0.44-1.07)	0.800	0.0%
ER-/PR-	6	0.90 (0.78-1.04)	0.913	0.0%
P-heterogeneity[a]=0.222				
Type of controlsg				
Hospital based	7	0.96 (0.87-1.06)	0.041	44.7%
Population based	11	0.91 (0.81-1.04)	0.318	14.3%
P-heterogeneity[a]=0.510				

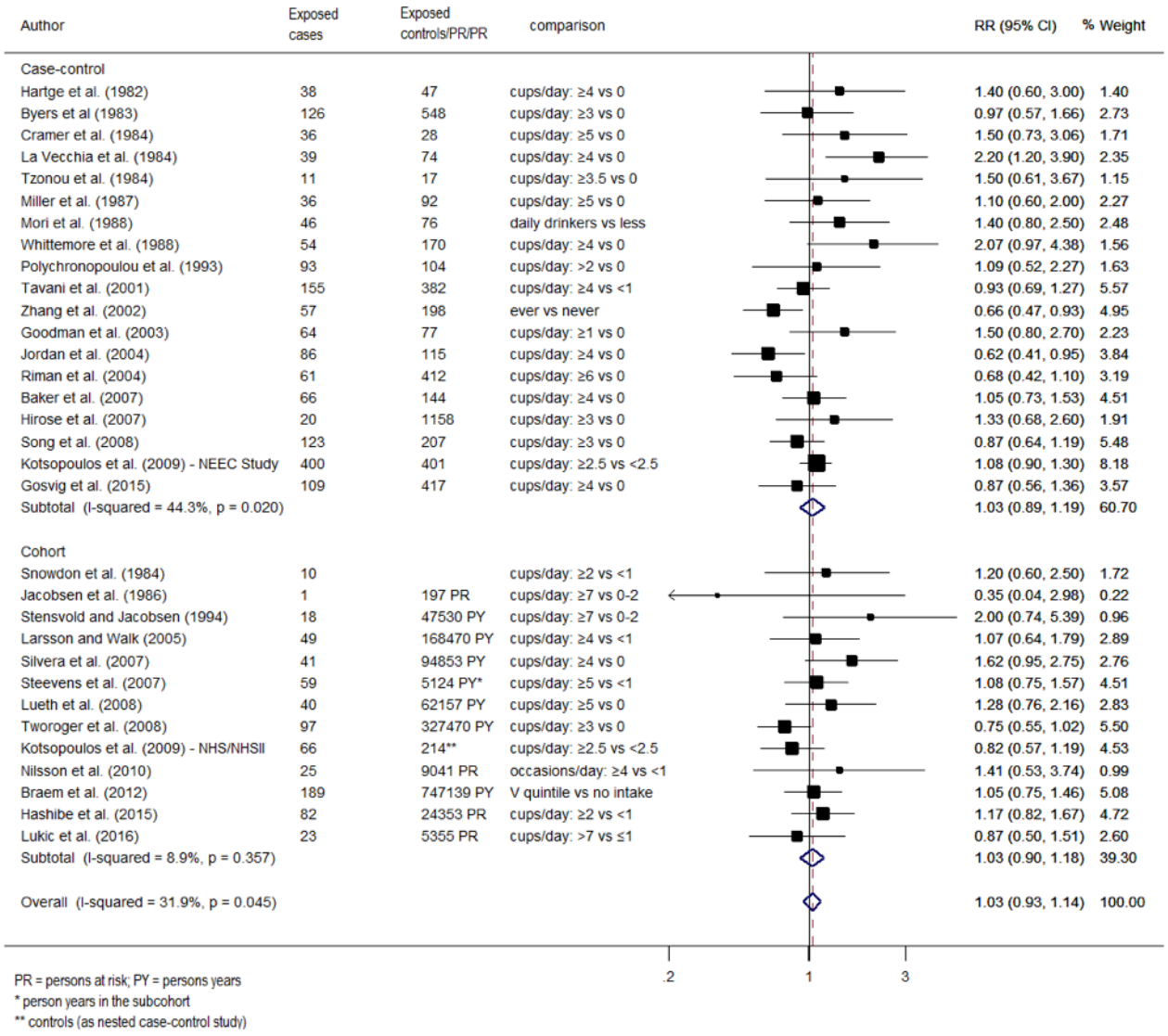
[a] Among strata; b Including one study from Israel [28]; [c] One study conducted within the European Prospective Investigation into Cancer and Nutrition cohort [21], which included participants from 10 European countries, was not considered in the stratified analysis by European location. [d] p value comparing summary estimates across studies from North America, Asia, and Europe. [e] This analysis included estimates from a study in which age at breast cancer (<49 years versus >55 years) was considered a proxy of menopausal status [57]. Estimates from a cohort in which over 96% of women were postmenopausal at baseline [59] and from a cohort of women ≥55 years of age at baseline [22] were included in the stratum of post-menopausal breast cancer. [f] Normo-weight / overweight subjects were defined, respectively, as follow: body mass index (BMI) <25 / ≥25 kg/m² in 2 studies [51-52], BMI≤25 / >25 kg/m² in 2 studies [48,54], BMI<24 / ≥24 kg/m² in one study [43], and BMI≤26.5 / >26.5 kg/m² in one study [40]. [g] Only for case-control studies; Studies using neighborhood controls as well as family-based controls were considered together with those using population-based controls.

of caffeinated coffee (highest vs lowest intake) with ovarian cancer risk was 1.08 (95%CI 0.84-1.38) with moderate-to-high between study heterogeneity (I2 =62.4%, p-heterogeneity, 0.021) (data not shown).

Subgroup analysis

In Table 3 summary RRs (95% CI) of ovarian cancer comparing the highest versus the lowest coffee consumption are shown by strata of selected covariates. No significant

FIGURE 2. Relative risks (RRs) and 95% confidence intervals (CI) of ovarian cancer for the highest versus the lowest coffee drinking category from case-control and cohort studies, and from all the studies combined. The combined RRs and 95% CI were calculated using the random-effects models.



heterogeneity was found by caffeine content, geographic area and menopausal status.

Histological type of the neoplasm (serous/mucinous/endometrioid/clear cell) or severity of disease (invasive/borderline) was reported in 7 studies [17, 24, 74, 84, 88-90]. There was no evidence of heterogeneity across strata of either tumour characteristic.

There was a significantly increased risk among hospital-based, case-control studies (RR: 1.18, 95%CI 1.00-1.39) and among studies published before the year 2000 (RR: 1.37, 95%CI 1.12-1.69), while no association was observed among population-based case-control studies (RR: 0.95, 95%CI 0.78-1.17) or among more recent studies (RR: 0.96, 95%CI 0.86-1.06). There was evidence for heterogeneity according to year of publication (p-heterogeneity, 0.003).

Figure 3 shows the cumulative meta-analysis for ovarian cancer for the highest versus the lowest coffee intake by year of publication. The cumulative RR for papers published up to 2000 was significantly above unity (RR: 1.37, 95%CI 1.12-1.69), while it levelled down to unity afterwards.

Sensitivity analysis and publication bias

The influence analyses did not reveal any notable change in the summary estimate with the exclusion in turn of any study, with summary RRs varying between 1.01 and 1.05 (not significant).

The funnel plot of RRs for ovarian cancer studies is

shown in Supplementary Figure 5. P-values for Begg's and Egger's tests were both 0.008, indicating a potential for publication bias owned to the inclusion of published studies with rather imprecise positive associations of coffee intake with ovarian cancer risk (published before 2000) and the lack of similar studies showing inverse associations (lower left part of the funnel is missing in contrast to the lower right part of the funnel).

DISCUSSION

In the present meta-analyses of all published data up to June 2016, including 41 studies and 76,728 breast cancer cases, and 32 studies and 13,111 ovarian cancer cases, we found no overall association between coffee consumption and breast or ovarian cancer risk. For both cancer sites, results were consistent among case–control and cohort studies, across different geographical areas, and for pre- and post-menopausal women. For breast cancer, summary estimates were also consistent in strata by BMI, receptor status, as well as among case-control studies with hospital-based or population-based control subjects. For ovarian cancer the null association with coffee intake was also consistent in strata defined by severity and histologic type of disease.

Our findings are in agreement with reports of international research bodies [7]. The recent WCRF reports [4, 5] were based on analyses of cohort studies only, published up to 2016 and 2012 for breast and ovarian cancers respectively, and their evaluation of the evidence for coffee intake in relation to both cancers was "limited-no conclusion". In our study we have analysed also all case-control studies published up to mid-2016 and we added three new cohort studies. Our results based on all available evidence up to June 2016, agree, further supplement and more precisely quantify those produced by the WCRF.

Our findings are also in agreement with recently published meta-analyses. For breast cancer previous meta-analyses including case-control and cohort studies [10, 12, 13] or cohort studies only [11, 14] had a few methodological limitations in the inclusion/exclusion of studies and eventually reported, not statistically significant weak inverse associations for the highest vs lowest coffee intake (RRs of around 0.95 overall) [10, 12, 13]. For ovarian cancer, previous meta-analyses using either cohort and case-control studies [17], or, cohort studies only [14,18] reported summary RRs close to unity similarly to our overall pooled estimate. Pooling RRs from case-control studies published up to 2007 resulted in a RR of 1.15 (95% CI 0.89, 1.47) [17] whereas our pooled estimate including three additional case-control studies published after 2007 [24, 78, 91] was close to unity. None of the cohort studies found a statistically significant relation in ours and in previous meta-analyses [14, 17, 18].

We observed a weak positive association of ovarian cancer risk with increased coffee consumption among the 12 studies (including only 3 prospective investigations) published before 2000, as well as among case–control studies with hospital-control patients, mostly published before 2000. This apparent inconsistency with the overall null association, may be due to false-positive results documented in earlier studies, as well as, selection bias associated with the hospital-based case-control design. Moreover, the significant p values from Begg's and Egger's tests indicated publication bias, probably due to the inclusion of older studies (published before 2000). According to this type of publication bias, however, the RR estimated from our meta-analysis is likely an overestimation of the "true" association of coffee intake with ovarian cancer risk and, therefore, our results further support the absence of such a relation.

We also performed meta-analyses for decaffeinated coffee intake. For breast cancer we found a null overall association in agreement with results of the only meta-analysis which investigated this relation [13]. For ovarian cancer the pooled RR was indicative of an inverse overall association (RR=0.83, 95% CI 0.71-0.96), but with no statistically significant heterogeneity across strata by caffeine content. Two of the 9 studies included in this meta-analysis [85, 90] showed decreased risk with increased decaffeinated coffee consumption, whereas the seven additional studies reported null associations. No previous meta-analysis of ovarian cancer has investigated this relation.

Coffee contains many bioactive compounds such as phenolic acids with strong antioxidant properties and cafestol and kahweol with anticarcinogenic activity [98] and, inverse association of this beverage with liver and endometrial cancer risk has been demonstrated [8, 99]. Moreover, previous studies suggested that coffee and caffeine are inversely associated with sex hormones (testosterone and estradiol) [100, 101], higher levels of which may be associated with increased breast and ovarian cancer risk [102-104]. On the other hand coffee contains also acrylamide which has been suggested to increase breast and ovarian cancer risk [105]. The results of our meta-analysis demonstrating no association between the consumption of coffee and risk of breast or ovarian cancer may reflect a combination of positive and negative effects.

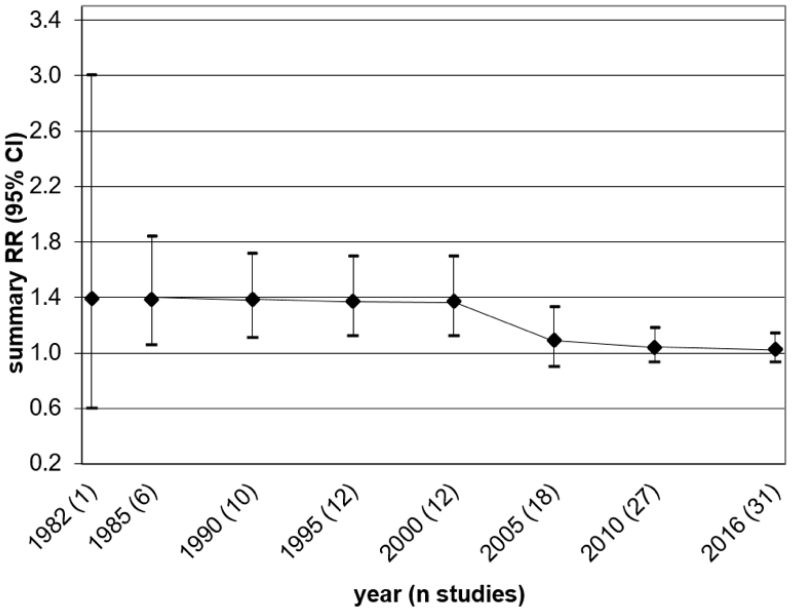
In our meta-analysis, we pooled RRs for the highest versus the lowest coffee drinking categories based on the study-specific cut-offs and therefore the "exposed" category (highest consumption) varied across studies. Nevertheless, this approach has been adopted by previous meta-analyses of coffee and various outcomes. We did not perform a dose-response meta-analysis since the null associations were consistent in overall and subgroup analyses. Our findings showed no material differences across different geographical locations with distinctly

TABLE 3. Summary relative risks (RRs) and 95% confidence intervals (CI) of ovarian cancer for the highest versus the lowest coffee drinking category in strata of selected covariates.

	N studies	RR (95% CI)	P-heterogeneity among studies	I^2
Type of coffee				
Caffeinated	6	1.08 (0.84-1.38)	0.021	62.4%
Decaffeinated	9	0.83 (0.71-0.96)	0.826	0.0%
P-heterogeneity[a]=0.076				
Geographic area				
North Americab	14	1.06 (0.94-1.20)	0.236	19.5%
Asia	3	1.02 (0.59-1.76)	0.034	70.3%
Europec	13	1.04 (0.89-1.22)	0.273	16.9%
Northern Europe	8	0.96 (0.79-1.16)	0.496	0.0%
Southern Europe	4	1.29 (0.83-2.02)	0.076	56.3%
Australia	1	0.62 (0.41-0.95)	-	-
P-heterogeneity[a,d]=0.121				
Menopausal status				
Pre-menopause	3	1.08 (0.67-1.73)	0.116	49.3%
Post-menopause	6	0.94 (0.72-1.22)	0.018	60.9%
P-heterogeneity[a]=0.604				
Severity of cancer				
Invasivee	7	0.95 (0.72-1.27)	0.008	65.4%
Borderline	3	1.07 (0.67-1.73)	0.731	0.0%
P-heterogeneity[a]=0.673				
Histologic typef				
Serous	6	0.90 (0.61-1.32)	0.019	63.0%
Mucinous	4	1.21 (0.64-2.31)	0.532	0.0%
Endometrioid	3	1.08 (0.63-1.84)	0.652	0.0%
Clear cell	2	1.44 (0.63-3.29)	0.292	9.9%
P-heterogeneity[a]=0.713				
Type of controlsg				
Hospital based	11	1.18 (1.00-1.39)	0.404	4.1%
Population based	8	0.95 (0.78-1.17)	0.066	47.2%
P-heterogeneity[a]=0.224				
Year of study publication				
<2000	12	1.37 (1.12-1.69)	0.672	0.0%
>=2000	19	0.96 (0.86-1.06)	0.106	29.5%
P-heterogeneity[a]=0.003				

[a] Among strata; [b] Including one study from Hawaii [87]. [c] One study conducted within the European Prospective Investigation into Cancer and Nutrition cohort [21], which included participants from 10 European countries, was not considered in the stratified analysis by European location. [d] p value comparing summary estimates across studies from North America, Asia, Europe and Australia. [e] For one study we pooled RR for invasive serous, mucinous, endometrioid and clear cell type to obtain the RR for all invasive ovarian cancers [90]. [f] Invasive cancer only. [g] Only for case-control studies. One study including hospital and population controls and calculating RRs using separately the two types of controls was considered in both strata [16], whereas one study with 40% of hospital and 60% of population controls was excluded from the stratified analysis [86].

FIGURE 3. Cumulative meta-analysis for ovarian cancer for the highest versus the lowest coffee intake by year of publication.



different patterns of coffee intake (e.g. Asian, European, Northern American studies). We were not able to account for type of coffee beans (Robusta versus Arabica), brewing methods, preparation and cup size, characteristics that may influence the chemical composition of coffee, as the vast majority of the included studies did not provide such information. Only an early case-control study [62] and a recent cohort study [57] investigated separately the role of brewed/instant and filtered/boiled coffee on breast [57, 62] and ovarian cancer risk [57]. For breast cancer Schairer et al [62] did not find any association with either coffee type, whereas Nilsson and colleagues [57] reported decreased risk for boiled (overall) and filtered coffee (among postmenopausal women only) and increased risk for filtered coffee among pre-menopausal women. For ovarian cancer Nilsson et al [57] did not observe clear differences of the association of boiled and filtered coffee.

Our study is the most up-to-date meta-analysis of breast and ovarian cancer as it includes articles published up to June 2016. Additional studies published up to January 2017 are for breast cancer two case-control studies by Cauchi et al (2016) [106] and Wielsoe et al (2016) [107] of 200 and 60 cases, which found RRs of 0.90 (95% CI 0.81-1.00) for every cup/month of coffee intake and 0.52 (0.13; 2.07) for >3 cups/day versus <1 cup/day, respectively. For ovarian cancer, only one Canadian case-control study was published (Leung et al 2016) including 524 cases and found a RR of 0.82 (95% CI 0.56-1.19) for >90 versus <50 adult lifetime cup-years of coffee. Thus, these studies will not materially modify our overall summary RR estimates.

Major strengths of our study are the in depth systematic review and the large number of studies included, allowing for several subgroup analyses. However, some limitations should also be acknowledged. The studies included in our meta-analysis may have various sources of bias. Misclassification of coffee consumption due to self-reported assessment is likely in the original studies but this would be non-differential among cohort studies where information is collected long time before breast/ovarian cancer diagnosis. For case-control investigations, coffee assessment was based on patients' reports which may be different from the reports by the control subjects. However, the similar RR estimates in case–control and prospective studies for both cancer sites are against such hypothesis. Also, recall of coffee drinking has been shown to be satisfactorily valid [109, 110].

Other types of selection or information bias in case-controls studies cannot be excluded. For breast cancer, however, results were consistent among hospital-based, population-based case–control studies and prospective investigations, minimizing the probability of major bias that may have appreciably influenced our results. For ovarian cancer the apparent differentiation in RRs estimated for hospital-based and population-based case-control studies is probably attributed to earlier imprecise studies. Nevertheless the pooled associations for coffee intake were similar among population-based and cohort studies for this cancer site also. With respect to residual confounding, the well-accepted risk factors for breast and ovarian cancer were included in many studies, especially the most recent ones, and we used in our meta-analyses multivariate RRs adjusted for all available covariates.

In conclusion, our systematic meta-analyses of case–control and cohort studies provide strong, quantitative

evidence to support the IARC evaluation that there is evidence suggesting lack of carcinogenicity of the female breast cancer due to coffee consumption, even at high doses. For ovarian cancer, there appears to be no association with coffee consumption, and the evidence is more inconsistent particularly with regards to the results of earlier studies, which is also in agreement with the IARC evaluation of 'inadequate evidence'. Taken together the accumulated evidence regarding the association of coffee with endometrial cancer risk, this widely consumed beverage appears to be unrelated to women's hormonal-related cancer excess risk.

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Conflicts of Interest

Carlo La Vecchia is a member of the Advisory Board of International Sweeteners Association (ISA).

The rest of the authors declare no conflicts of interest.

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Supplementary

TABLE1. Details on handling specific studies in the stratified meta-analyses of coffee consumption with breast and ovarian cancer risk.

In the stratified analysis by menopausal status, a cohort of women ≥55 years of age at baseline [22] and a cohort in which over 96% of women were postmenopausal at baseline [59] were included in the stratum of post-menopausal breast cancer. For the stratified analysis by histological type of ovarian cancer the RRs for the New England Case Control (NECC) Study were considered from the publication by Kuper et al. [84], as the most recent publication by Kotsopoulos et al. [78] (included in the main analyses), did not provide such separate estimates. In stratified analyses by BMI, for the Swedish Mammography cohort [41] and for the multicenter European Investigation into Cancer and nutrition cohort (EPIC) [21] cohort (included in the main analyses) we used the papers based on the same cohorts but with either shorter follow-up [48] or confined to Netherlands [54], since RRs according to BMI strata were not reported in the more complete articles. Normo-weight and overweight subjects were defined, respectively, as follows: body mass index (BMI) <25 versus ≥25 kg/m2 in two studies [51, 52], BMI ≤25 versus >25 kg/m2 in two studies (48, 54), BMI <24 versus ≥24 kg/m2 in one study [43], and BMI ≤26.5 versus >26.5 kg/m2 in one study [40] . For the Ganmaa et al [51] study which reported RRs for coffee intake in the BMI 25-29 and ≥30 kg/m2 strata, a summary RR for overweight women was obtained by pooling the indicated RRs with a fixed effects model. Similarly, in the study by Tavani et al [40] RRs in the strata of BMI <23.2 kg/m2 and 23.2-26.5 kg/m2 were pooled in order to generate a result for normo-weight women

FIGURE 1. Selection strategy to identify studies that were included in the meta-analysis of coffee intake with breast and ovarian cancer risk.

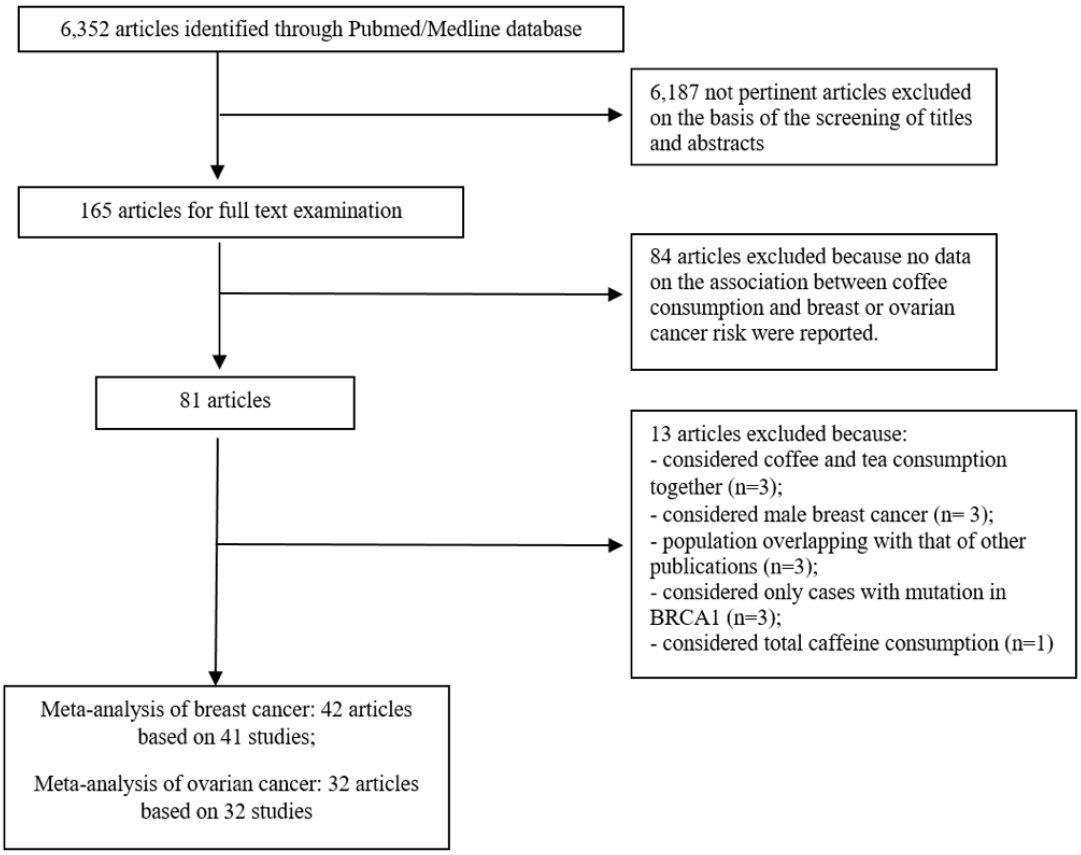

FIGURE 2. Relative risks (RRs) and 95% confidence intervals (CI) of breast cancer for the highest versus the lowest decaffeinated coffee drinking category. The combined RRs and 95% CI were calculated using the random-effects models.

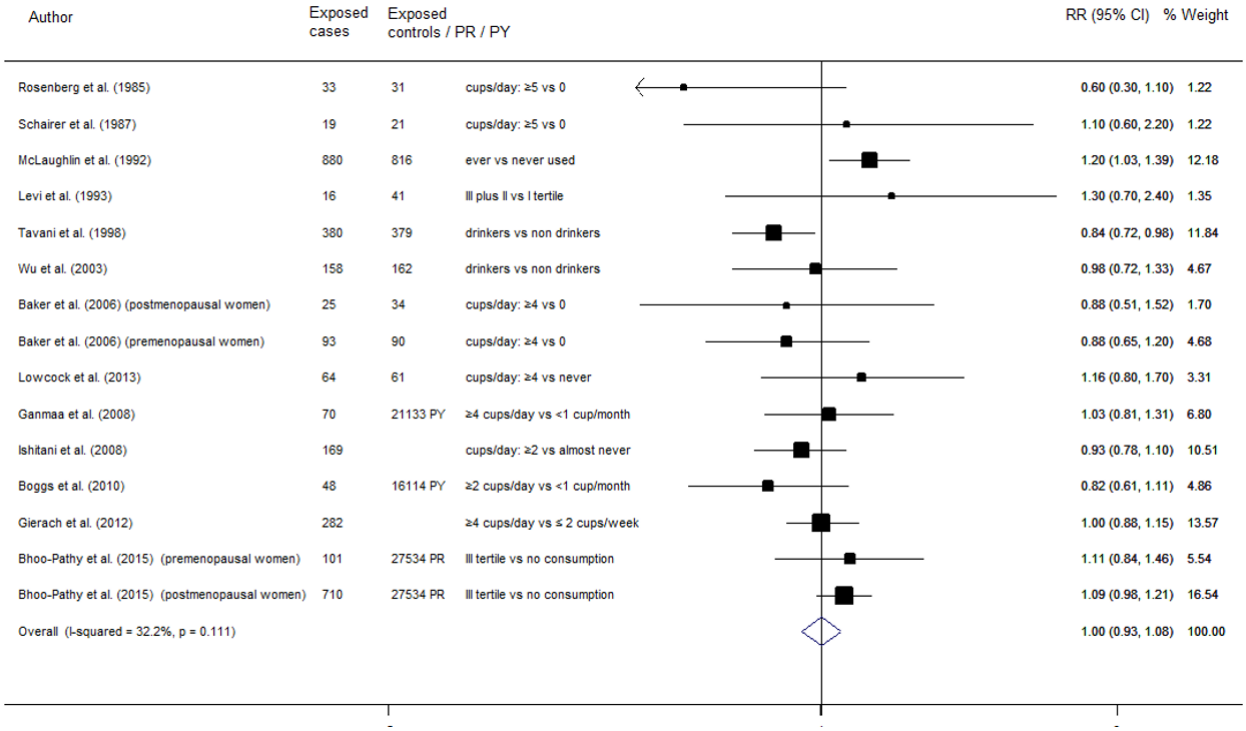

FIGURE 3. Funnel plot for the assessment of publication bias in the 40 studies included in the meta-analysis of coffee intake with breast cancer risk (p for Egger test 0.877; p for Begg test 0.753). Dashed diagonal lines indicate 95% CI

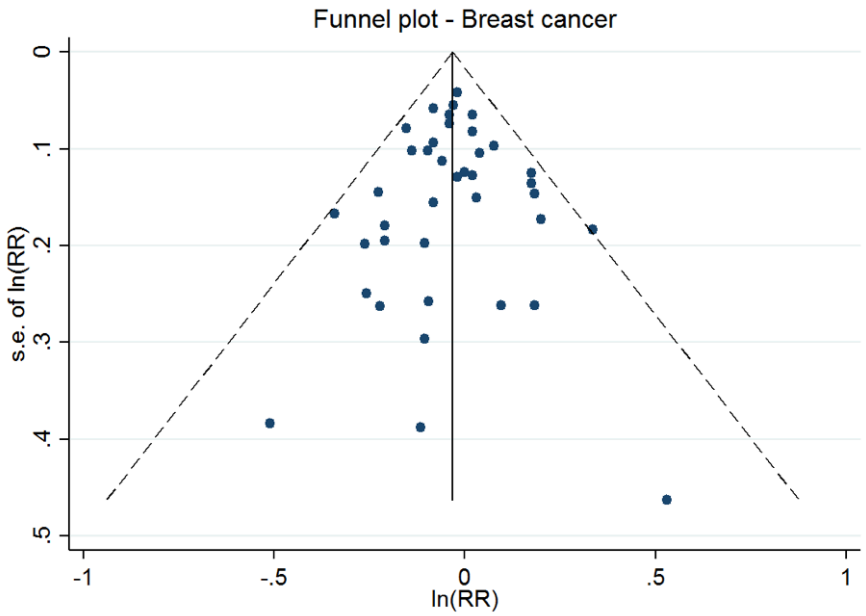

FIGURE 4. Relative risks (RRs) and 95% confidence intervals (CI) of ovarian cancer for the highest versus the lowest decaffeinated coffee drinking category. The combined RRs and 95% CI were calculated using the random-effects models.

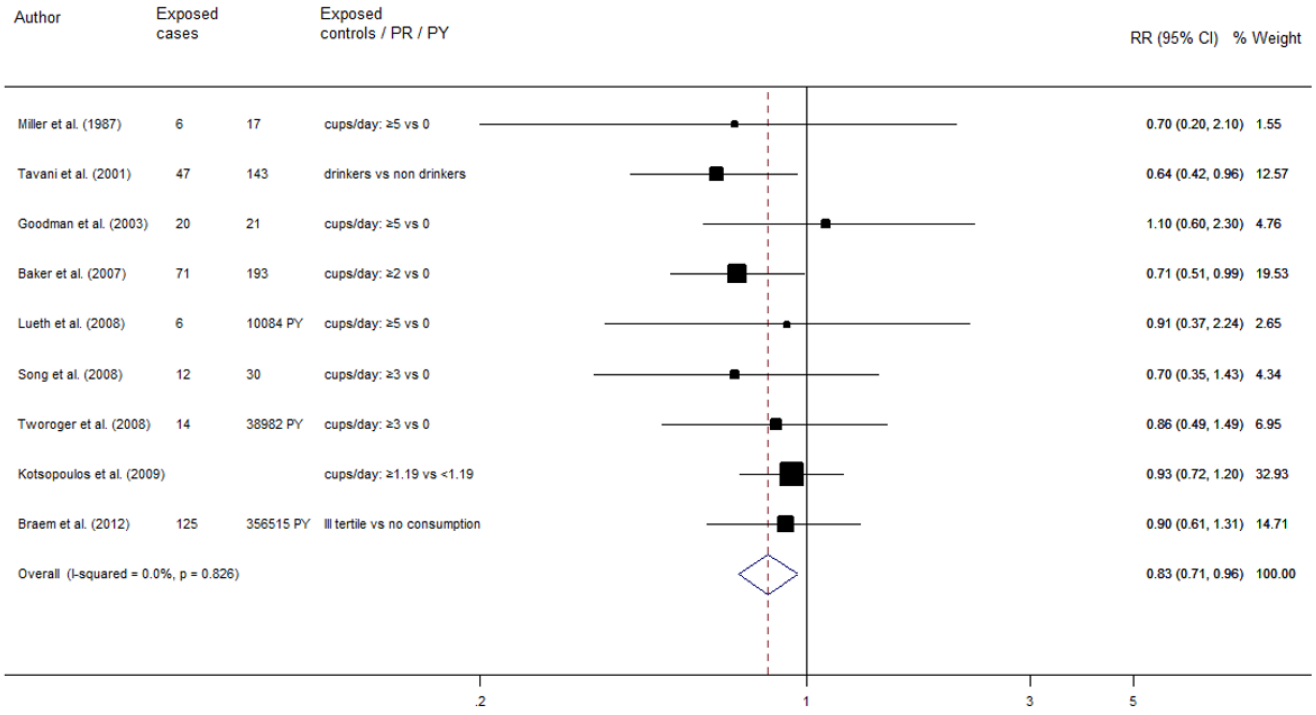

FIGURE 5. Funnel plot for the assessment of publication bias in the 31 studies included in the meta-analysis of coffee intake with ovarian cancer risk (p for Egger test 0.008; p for Begg test 0.008). Dashed diagonal lines indicate 95% CI.