

# Coffee Consumption and Cancer Risk: An Assessment of the Health Implications Based on Recent Knowledge

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## Highlights of the Study

- Coffee consumption is inversely associated with liver cancer and breast cancer among postmenopausal women.

## Keywords

Coffee consumption · Cancer risk · Antioxidants · Anti-inflammatory agents

## Abstract

A significant number of studies suggest that coffee consumption reduces cancer risk. This beneficial effect is usually ascribed to the presence of polyphenolic antioxidants and anti-inflammatory agents, including caffeine, cafestol, kahweol, and chlorogenic acids. To summarize recent literature on this subject, we performed a bibliographic search in PubMed and Embase over the period January 2005 to December 2020 to identify cohort studies and meta-analysis (with data collection ensuring quality of selected reports) that could provide quantitative data on the relationship between coffee consumption and common cancers. The totality of eligible scientific articles supports the evidence that coffee intake is inversely associated with risk of hepatocellular cancer and, to a slight extent, risk of breast cancer among postmenopausal women. As to the association with other organs, including the esophagus, pancreas, colorec-

tum, kidneys, bladder, ovaries, and prostate, the results are less clear as reports reveal conflicting results or statistically nonsignificant data. Therefore, this overview does not provide broad-based conclusions. Important uncertainties include general study design, inhomogeneous patient sampling, different statistical analysis (deliberate), misreporting of socioeconomic status, education, coffee-brewing methods, consumption of caffeinated or decaffeinated coffee, smoking habits, and alcohol intake. Clearly, more epidemiologic research needs to be conducted before solid science-based recommendations can be made with regard to coffee consumption.

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## Introduction

Differences in dietary patterns across the world suggest that several nutritional compounds may improve human health. A significant number of investigations suggest that coffee consumption diminishes cancer risk. This phenomenon has attracted the interest of health profes-

sionals more so as coffee consumption has dramatically increased over the past few decades due to increased prosperity and commercial interest [1]. Indeed in 2011, it was estimated that 500 billion of cups of coffee were being consumed annually [2]. It is commonly regarded that oxidative stress and inflammation are the basis of many disabling processes, including carcinogenesis. In this context, the beneficial effects of coffee have been mainly attributed to the abundant presence of polyphenolic antioxidants and anti-inflammatory agents, including caffeine, cafestol, kahweol, and chlorogenic acids [3], which are part of more than thousand (mostly unidentified) different chemicals in brewed coffee [4], and various articles have dealt with the beneficial features of these polyphenolic molecules [5–7]. Despite these beneficial characteristics, cafestol and kahweol appear to increase cardiovascular risk, presumably as these molecules raise the concentration of serum lipids [8]. In boiled, unfiltered coffee, these diterpenes have been found to be responsible for this increase [2].

This narrative review concentrates on the topic of cancer risk in relation to coffee consumption. For this, we present key eligible organ-specific articles and epidemiologic data, dating from January 2005 to December 2020, in the clinical context of solid malignancies including cancer of the breast, liver, esophagus, stomach, pancreas, colorectum, kidney, bladder, prostate, and ovaries. Data were extracted using the keywords coffee consumption, cancer risk, and analysis. The literature search in the electronic databases PubMed and Embase resulted in 463 bibliographic studies. Of these, 105 articles were selected on the appraisal of titles, abstracts, and their features regarding coffee consumption in the light of cancer risk and specific statistical analysis. First, however, we will describe the relevant biomedical properties of the mentioned bioactive compounds that have been put forth to link coffee intake with cancer risk.

### **Important Compounds in Coffee in Relation to Cancer Risk**

#### *Caffeine*

Caffeine, a competitive antagonist of the neurotransmitter adenosine on the adenosine receptor subtypes A1, A2A, and A2B, belongs chemically to the group of xanthenes. Generally, this antagonism stimulates physical and cognitive abilities [9]. After ingestion, caffeine is for the greater part absorbed by the small intestine and distributed over all tissues, including the brain. Its

metabolism occurs mainly in the liver through P 450 isoform CYP 1A2 into 3 metabolites: paraxanthines (increasing lipolysis), theobromine (dilating the vascular system and increasing diuresis), and theophylline (relaxing bronchial muscles) [10]. Caffeine inhibits tumor necrosis factor- $\alpha$ , leukotriene synthesis, and other inflammation mediators such as interleukin-6, interleukin-8, and prostaglandin E2, reducing inflammatory processes [1, 11, 12]. Caffeine, together with other polyphenols, has been shown to possess a distinct antioxidant response element activating potential, mitigating oxidative stress [13–15].

#### *Cafestol and Kahweol*

The structurally related molecules cafestol and kahweol are natural diterpenes in coffee. Various studies have confirmed that both compounds act as anti-inflammatory and antiangiogenic agents [16, 17]. Whereas inflammatory angiogenesis is a critical hallmark of the expansion of malignant cells in the tumor environment, these beneficial profiles of these naturally occurring coffee ingredients are the subject of ongoing investigations [18]. Indeed, experimental and human studies have shown that cafestol and kahweol are potential agents for arresting tumor growth by blocking or diminishing neoangiogenesis [19, 20].

#### *Chlorogenic Acids*

Chlorogenic acids (acids between caffeine and quinic acids) represent a major component of plant polyphenols. Among the phenolic compounds in coffee, chlorogenic acids are present in the highest concentrations ranging up to 98% [21]. In spite of this high level, the native compounds are found in low concentrations in the blood due to extensive metabolic transformations [22]. In general, the anticancer capacity of these acids is attributed to the quenching of free radicals and singlet oxygen, inhibiting the formation of carcinogens. Other health effects are linked to stimulating the proliferation and activation of T cells, NK cells, and macrophages, which delay and possibly inhibit the growth of cancer cells [23, 24].

#### *Clinical Aspects of Coffee Consumption and Cancer Risk*

To obtain an adequate picture of the cancer risks, we gave preference to the most informative and essential articles, often consisting of cohort studies and meta-analysis, rather than summing up all available data retrieved from the literature.

### Breast Cancer

We found 6 eligible studies that assessed the risk of breast cancer. A study by Hirvonen et al. [25] in 4,396 women found no association between consumption of coffee and risk for breast cancer. Also, a large study conducted on 67,703 women with a median follow-up of 11 years and a median intake of 2.2 cups/day showed no relationship between coffee intake and breast cancer risk [26]. By contrast, a cohort study of 85,987 participants during the years 1980–2002 found a significant inverse association of caffeine intake with breast cancers among postmenopausal women for those who consumed 4 or more cups/day relative to those who drank less than 1 cup/month (RR 0.88; 95% confidence interval (CI) 0.79–0.97). A significant trend was established for increasing amounts of caffeine intake ( $p = 0.03$ ) [27]. Likewise, the European Prospective Investigation into Nutrition and Cancer (EPIC) study, in which 335,060 women participated during 1992–1994 and followed up until 2010, found an association between coffee intake and lower postmenopausal breast cancer risk (adjusted HR = 0.90; 95% CI 0.82–0.98) [28]. Also the Spanish SUN project found a slight indication of an inverse association between coffee consumption of more than 1 cup caffeinated coffee per day and breast cancer risk in a prospective cohort during 115,802 person-years of follow-up in 10,812 middle-aged women (HR 0.44; 95% CI 0.21–0.92) [29]. This relationship was not found for women who used decaffeinated coffee [30]. By contrast, a recent follow-up study among more than 57,000 postmenopausal women study over 16 years did not support an association between coffee consumption and invasive breast cancer, comparing consumption of 2 or more cups per day with 1 cup per month [31]. Overall, recent epidemiologic studies involving large numbers of participants provide only limited evidence that coffee intake is beneficially associated with breast cancer risk.

### Hepatocellular Cancer

In 2007, Tanaka et al. [32] published an investigation for which 209 incident hepatocellular cancer (HCC) cases and 1,308 community controls were recruited. This questionnaire-based study revealed a decreasing risk with increasing amounts of coffee consumption: adjusted odds ratio (OR) for 3 or more cups/day compared to no use 0.10 (95% CI 0.04–0.24) and  $p$  for trend  $<0.001$  for occasional use, 1–2 cups/day, and 3 or more cups/day. This study formed the overture to other investigations involving Asian subjects, namely, a case-control study by Leung et al. [33] and cohort studies by Inoue [34] and Johnson

et al. [35] which confirmed the beneficial effect of coffee. Also an Italian case-based study by Montella et al. [36] supported this evidence. An outstanding study by Hu et al. [37] included 60,323 Finnish participants; during a median follow-up period of 19.3 years, 128 participants were diagnosed with incident primary liver cancer. On the basis of their data, the authors reported that for individuals who drank 8 or more cups/day ( $n = 9,775$ ), the adjusted hazard ratio was 0.32 (95% CI 0.16–0.62) and  $p$  for trend = 0.003 (0–1, 2–3, 4–5, 6–7, 8, or more cups/day).

Three meta-analyses [38–40] and 1 pooling study [41] are in line with the abovementioned outcomes, all showing that coffee intake was inversely related to the risk of liver cancer. The latter, most striking investigation by the Liver Cancer Pooling Project, dealt with information obtained from a consortium of 9 US-based cohorts. The data from 1,212,837 individuals (HCC incidence = 860) demonstrated that higher coffee consumption was associated with lower HCC risk (HR  $>3$  cups/day vs. nondrinkers 0.73 (95% CI 0.53–0.99) and  $p$  for trend  $<0.0001$ ). The association was stronger for caffeinated coffee ( $>3$  cups/day vs. nondrinkers RR 0.71 (95% CI 0.50–1.01) than for decaffeinated coffee ( $>3$  cups/day vs. nondrinkers RR 0.92 (95% CI 0.55–1.54). The abovementioned outcomes have been confirmed in a most recent analysis of 20 case-control or prospective studies [42]. Although significant heterogeneity between studies was observed, the relative risk amounted to 0.69 (95% CI 0.56–0.85;  $p < 0.001$ ) as to increments of 1 cup of coffee drinking per day demonstrating a decrease of cancer risk with higher doses of coffee consumption. Overall, available epidemiologic evidence supports the claim that coffee intake reduces the incidence of primary hepatocellular cancer and that there is a significant dose response between coffee consumption and liver cancer risk.

### Esophageal Cancer

Four important epidemiologic studies on the subject have been published over the past 10 years. In a study by Naganuma et al. from 2008, an inverse association of esophageal cancer with coffee consumption was found [43] for more than 1 cup/day compared to no coffee use (HR 0.51; 95% CI 0.33–0.77). However, this inverse relationship has not been supported by later prospective cohort studies, including the ones by Tverdal et al. [44] ( $n = 389,624$ ; average follow-up 14.4 years) and Zamora-Ros et al. [45] ( $n = 442,143$ ; average follow-up 11.1 years). The latter study comprised participants from 9 countries of the EPIC study. During their period of study, 339 par-

ticipants developed esophageal cancer, but no clear association was found, although a dose-related decline was suggested in men comparing the extreme tertiles (HR 0.46; 95% CI 0.23–0.93;  $p$  for trend 0.02). This latter finding is not in contrast with a meta-analysis performed by Zhang et al. [46]. These researchers identified 11 studies fulfilling their inclusion criteria with participants from East Asia, Europe, and America. The selected studies contained 208 cohort studies and 2,420 case-control studies, and subjects were stratified into heavy coffee drinkers and light or no coffee drinkers. The combined OR for heavy coffee drinkers was 0.93 (95% CI 0.73–1.12) compared to the light or no coffee drinkers. Although no association whatsoever was found between those 2 groups, an interesting geographical difference was detected; an inverse association between coffee consumption and esophageal cancer was found in East Asian subjects (OR = 0.64; 95% CI 0.44–0.83) but not in the participants from Europe and America (OR = 1.05; 95% CI 0.81–1.29). Thus, until this latter finding is confirmed, it is safe to conclude that there is no compelling support for a beneficial effect of coffee consumption on the risk for esophageal cancer.

#### *Stomach Cancer*

A large questionnaire-based study comprising 96,024 individuals by Hashibe et al. [47] from 1992 to 2001 focused on specific cancers, including gastric cancer. During this period of follow-up, 136 stomach cancers were detected. The relative risk per cup adjusted for race, education, and smoking and drinking habits amounted to 1.04 (95% CI 0.95–1.15) and a  $p$  for trend of 0.9095. On the other hand, a recent meta-analysis, involving 22 articles of prospective cohort or case-control design, by Xie et al. [48] reporting on 7,631 cases of stomach cancer and 1,019,693 controls, indicated that an increase in coffee consumption was associated with a decrease in stomach cancer. For example, pooled data for 3–4 cups/day versus nondrinkers revealed an RR of 0.88 (95% CI 0.76–1.03) ( $p$  for trend not indicated). This study is in contrast with 4 other recent articles reporting on meta-analysis of prospective studies. One study [49] demonstrated an increased risk in US studies (RR 1.36; 95% CI 1.06–1.74). Li et al. [50] comparing the highest with the lowest coffee consumption found the same statistical numbers, viz. RR of 1.36 (95% CI 1.06–1.75) for participants in the USA. These researchers pooled data of 13 prospective studies ( $n = 1,372,811$ ) and found a 25% higher risk of gastric cancer in follow-up groups of 10 years or less (RR 1.25; 95% CI 1.01–1.55). Likewise, Zeng et al. [51] detected in

a subgroup analysis an elevated risk in the US population (RR 1.36; 95% CI 1.06–1.75) for high coffee consumption (6.5 or more cups/day). Similar outcomes were obtained by other researchers [52–54]. To add to this confusion, a recent British prospective cohort study over 7.5-year follow-up and 471,779 participants by Tran et al. [55] did not find a reduced risk of gastric cancer for an intake up to 5 cups/day (HR 1.03; 95% CI 0.97–1.09,  $p$  trend 0.30). Thus, there is no clarity on the possible reduction of the risk of stomach cancer. However, an increase for the risk of stomach cancer has been noticed, and this increase is especially evident in the US population.

#### *Pancreatic Cancer*

In 2015, Guertin et al. [56] published a large questionnaire-based prospective study estimating the risk of pancreatic cancer with coffee intake. They observed 1,541 first incident pancreatic cancers among 457,366 US adults with no missing data, occurring over approximately 4.2 million person-years of follow-up. After adjustment for smoking habits and additional covariates, they found no statistically significant relationship between coffee intake and person years for men ( $n = 275,328$ ;  $p = 0.55$ ) and women ( $n = 18,038$ ;  $p = 0.53$ ) for daily coffee doses ranging from 1 cup to 6 or more, both caffeinated and decaffeinated. These results are consistent with large studies by Bhoo-Pathy et al. [57] ( $n = 477,312$ ; mean follow-up 11.6 years) and Bidel et al. [58] ( $n = 60,041$ ; mean follow-up 18 years). Likewise, a meta-analysis based on 37 case-control and 17 cohort studies for a total of 10,594 pancreatic cancer cases or deaths found no significant association [59]. This analysis included 5,643 cases in North America, 1,886 cases in northern Europe, 1,932 cases in South America, 210 cases in eastern Europe, and 850 cases in Asia. Adjusted for smoking habits, the pooled RRs for the highest versus lowest category of coffee intake were 1.10 (95% CI 0.92–1.31) for case-control studies, 1.04 (95% CI 0.80–1.36) for cohort studies, and 1.08 (95% CI 0.94–1.25) for all studies. Most recently, a meta-analysis including 15 cohort studies also found no significant association between coffee intake and the risk of pancreatic cancer (RR 1.02; 95% CI 0.87–1.18) [60]. Intriguingly, a Swedish cohort study in twins dating from 2002, comprising 12,204 female and 9,680 male patients and 34 years of follow-up showed a protective effect of coffee consumption, most pronounced for 7 or more cups/day (RR 0.39 95% CI 0.17–0.89) [61]. However, on the basis of recent large studies, it is strongly suggested that there is no significant relationship between coffee consumption and pancreatic cancer risk.



### *Colorectal Cancer*

In 2012, the results of the NIH-AARP Diet and Health Study in 2 areas in the USA (Atlanta, GA and Detroit, MI) were published [62]; this investigation included 489,706 individuals of which 6,730 developed colorectal cancer over a median of 10.7 years of follow-up. This large prospective cohort study revealed that coffee intake was inversely associated with colon cancer. Hazard ratios for caffeinated coffee less than 1 cup/week were 0.97 (95% CI 0.86–1.10), 1 cup/day 0.99 (95% CI 0.84–1.11), 2–3 cups/day 1.01 (95% CI 0.92–1.10), 4–5 cups/day 0.91 (95% CI 0.80–1.00), and 6 or more cups/day 0.83 (95% CI 0.70–0.99), and the *p* for trend was 0.008. Similarly, the use of decaffeinated coffee showed a *p* for trend <0.001, and comparing the highest to the lowest consumption, the HR was 0.73 (95% CI 0.50–0.73). These beneficial results are in contrast with the outcomes of the aforementioned Prostate, Lung, Colorectal and Ovarian (PLCO) trial in which the multivariate adjusted RR for 9,268 participants and 116 cancer cases was 1.08 (95% CI 0.79–1.48), and *p* for trend equal to 0.229 was found for individuals drinking 4 or more cups/day [63]. This finding is in accordance with the data from the Women's Health Initiative Observational Study (*n* = 83,778; follow-up 12.9 years) in which the analysis showed an HR of 1.14 (95% CI 0.93–1.38) comparing nondrinkers to high coffee drinkers, pointing to an increased incidence risk [64]. The increased incidence risk with higher coffee consumption (4 or more cups/day) was previously found in a Japanese relatively long-lasting cohort study comprising 58,221 persons and a follow-up of 11 years. During this period, 687 participants developed colon cancer, and the HR for men was 1.57 (95% CI 0.57–2.55; *p* for trend 0.04) but was not significant for women [65]. A recent population-based case-control study [66] found that increasing coffee consumption was associated with lower odds of developing colorectal cancer (*p* for trend 0.001), and comparing the lowest (<1 cup/day) versus the highest dose (>2.5 cups/day), the OR was 0.46 (95% CI 0.39–0.54).

A meta-analysis published in 2009 [67] including 646,848 participants in 12 cohort studies showed no significant effect of coffee on colorectal cancer risk, comparing the high versus low consumption categories (RR 0.91; 95% CI 0.81–1.02). A 2011 meta-analysis of 40 independent cohorts revealed a summary RR of 0.89 (95% CI 0.97) for high coffee drinkers (6 or more cups/day) versus non/lowest drinkers (1 cup/day). By pooling the study-specific slopes, the summary RR for colorectal cancer risk with 1 cup/day increment was 0.97 (0.96–0.98) [68]. On the other hand, a 2010 study [69] found no significant

correlation by analyzing the pooled data of 13 prospective studies: for consumers of 6–8 cups/day versus nonconsumers, an RR of 1.07 (95% CI 0.89–1.30) was found. Li et al. [70] published a meta-analysis of 16 cohort studies in 2013 and demonstrated a slight overall inverse association with this disease (RR 0.94; 95% CI 0.88–1.01), which was more prominent in a subgroup of women. The most recent meta-analysis of 21 cohort studies [71] found a summary RR of 0.96 (95% CI 0.91–1.02; *p* for trend 0.175) evaluating the association between the highest versus lowest coffee intake.

Thus, the results of cohort studies mentioned are ambiguous with regard to beneficial effects of coffee consumption which was recently confirmed by Micek et al. [72]. An item of caution may well be the very recent finding that a cohort of more than 100,000 men and women, aged 47–96 years, consuming 2 or more cups per day of caffeinated coffee may increase rectal cancer risk (HR 1.37, 95% CI: 0.99–1.89, *p* trend 0.04) [73].

### *Kidney Cancer*

The relationship between coffee consumption and renal cancer has been analyzed in a case-control study in Italy [74]. A total of 767 individuals with incident renal cell carcinoma and 1,534 hospital-based controls were included in the study. The researchers compared drinkers of 4 or more cups/day with drinkers of 1 or fewer cups/day and found an OR of 1.02 (95% CI 0.73–1.43). Further analysis of a subgroup of never-smokers revealed an OR of 0.74 (95% CI 0.41–1.3) with no trend in risk with dose. Lee et al. [75] performed a pooled analysis of 13 prospective studies in 530,469 women and 244,483 men. The authors found a multivariate relative risk for 3 or more cups/day versus less than 1 cup/day of 0.84 (95% CI 0.67–1.05, *P* for trend 0.02), which made them cautiously conclude that coffee intake does not increase renal cancer risk. This risk has also been studied in the PLCO cohort [47], in which 318 kidney cancers were detected among 96,024 individuals from 10 centers across the USA during a follow-up of 10 years. Adjusted for smoking habits, age, gender, race, and education, the RR for 1–1.9 cups/day was 0.99 (95% CI 0.70–1.69), for 2 or more cups/day, 0.84 (95% CI 0.65–1.09), and for 4 or more cups/day, 0.43 (95% CI 0.20–0.93), whereas an overall dose response was not observed (*p* for trend 0.1015). A Canadian study in 8 provinces comprising 1,138 renal cancer cases and 5,039 population controls analyzed data obtained between 1994 and 1997. For the highest versus lowest quartiles, the OR was 1.33 (95% CI 1.07–1.66), indicating that higher coffee consumption was associated with renal cancer cases [76].

On the other hand, more recently, Huang et al. [77] found insignificant associations in both highest versus none or lowest coffee consumption in pooled data from 13 cohorts. Taken together, on the basis of recent studies comprising large numbers of participants, it can be cautiously concluded that coffee consumption is not associated with renal cell cancer risk.

#### *Bladder Cancer*

From the baseline information of the EPIC cohorts from France, the Netherlands, Germany, Sweden, and Denmark, the habitual coffee consumption of 233,236 participants was registered at recruitment. During the follow-up of 9.3 years, 491 individuals suffered from first primary urothelial cancer (more than 90% of bladder cancers arise from the endothelium) [78]. Analysis of specific types of beverages revealed no association between coffee intake and risk of endothelial cancer: comparing highest versus lowest intake in high-risk cancers revealed a hazard ratio of 1.07 (95% CI 0.71–1.61) and in low-risk cancers 1.08 (95% CI 0.76–1.53) with *p* for trend 0.84 and 0.69, respectively. Two meta-analyses of prospective cohort studies were published during our period of study. In 2011, a publication by Yu et al. [79] pooled the data of 9 cohorts and noted that coffee drinking was associated with a reduced risk of bladder cancer. The RR for low to moderate (2–3 cups/day) coffee drinkers was 0.79 (95% CI 0.67–0.91). The pooled data demonstrated a greater effect for men than for women. Another meta-analysis was published in 2012 by Zhou et al. [80] in which they showed the results of the pooling of 5 cohort studies with 700 disease cases and 229,099 participants. Smoking-adjusted RRs were 1.09 (95% CI 0.89–1.34) for 1 cup/day, 1.13 (95% CI 0.82–1.55) for 2 cups/day, 1.09 (95% CI 0.77–1.56) for 3 cups/day, and 1.01 (95% CI 0.69–1.48) for 4 cups/day (*p* for trend not provided). Thus, the cohort-based data mentioned above do not support clear evidence for a link between coffee intake and risk of bladder cancer.

#### *Prostate Cancer*

The abovementioned PLCO trial [47] was a large-scale study that also enabled the determination of the incidence of prostate cancer. In a cohort of 46,667 men, 3,037 prostate cancers were observed. With regard to coffee intake in this subcohort, the researchers found the following: for men drinking less than 1 cup/day, the RRs adjusted for age, race, and education appeared to be 0.99 (95% CI 0.97–1.01), for 1–1.9 cups/day 1.02 (95% CI 0.91–1.15), and for 2 or more cups/day 1.02 (95% CI 0.94–1.10). The

*p* for trend was 0.7020. Discacciati et al. [81] performed a dose-response meta-analysis for nonaggressive and fatal prostate cancer. For the last category, they found a significant but weak outcome showing a 12% reduced mortality risk for every 3 cups/day increase of coffee consumption (RR 0.88; 95% CI 0.81–0.97). Another meta-analysis [82] showed no significant association between coffee intake and prostate cancer risk using data of 4 cohort studies (RR 1.06; 95% CI 0.83–1.35). A recently published meta-analysis based on 105 prospective observational studies by Wang et al. [71] showed an inverse relationship on prostate cancer for the highest versus the lowest coffee intake (RR 0.89; 95% CI 0.84–0.93; *p* for trend 0.003). The summary relative risk for increment of 2 cups was 0.97 (95% CI 0.96–0.98) for prostate cancer. Another meta-analysis by Liu et al. [83] included 13 cohort studies with 34,105 cases of prostate cancer and 539,577 participants. Subgroup analysis of cancer grades revealed summary RRs for different coffee intake levels as follows: for nonadvanced cancer 0.89 (95% CI 0.83–0.96), for advanced 0.82 (95% CI 0.61–1.10), and for fatal disease 0.76 (95% CI 0.55–1.06). The authors suggest that coffee consumption may be associated with a reduced risk of prostate cancer (RR 0.91; 95% CI 0.85–95).

A study published in 2017 used an original approach. Taylor et al. [84] used 2 genetic variants in 2 loci robustly associated with caffeine intake as proxies for coffee consumption. A Mendelian randomization analysis in prostate cancer cases and controls, all of European genotype ancestry, were selected from the PRACTICAL consortium (practical.ccge.medschl.cam.ac.uk). During an average follow-up of 7.1 years, 1,754 death cases occurred in 14,010 men who contributed to this prostate cancer-specific analysis. Logistic regression was used to investigate associations of coffee-related single-nucleotide polymorphisms with prostate cancer-specific mortality. The hazard ratio with prostate cancer mortality was 1.03 (95% CI 0.98–1.08), suggesting that there is no clear evidence for an association between these coffee-linked polymorphisms and prostate cancer risk. Taken together, inconsistent information has been published on the link between coffee intake and prostate cancer risk for various tumor grades.

#### *Ovarian Cancer*

The Netherlands Cohort Study on Diet and Cancer observed 280 cases of first primary ovarian cancer in a subcohort of 2,083 postmenopausal women (55–69 years of age) during 13.3 years of follow-up over the period 1986–2000. The outcomes of this study were published by Steevens et al. [85] in 2007. The multivariable coffee increment, adjusted

for age, oral contraceptives, parity, and cigarette smoking, of 1 cup/day was 1.04 (95% CI 0.97–1.12). Analyzing the rate ratio over 0–0.9, 1–2.9, 3–4.9, and 5 or more cups/day provided a *p* for trend of 0.35. In the same article, the authors reported on a meta-analysis of 4 prospective cohort studies and found an OR of 1.18 (95% CI 0.97–1.14) for highest versus lowest coffee consumption. In a prospective Canadian cohort study (= 48,776) by Silvera et al. [86], 264 ovarian cancer patients were observed during a mean follow-up of 16.4 years. The evaluation of the highest versus no coffee consumption provided a hazard ratio of 1.62 (95% CI 0.95–2.75; *p* for trend 0.06). This outcome is in agreement with a prospective cohort study by Lueth et al. [87], who determined this relationship in 29,060 women followed for ovarian cancer from 1986 to 2004. In a multivariate model, they observed an increased risk in women who drank 5 or more cups/day of caffeinated coffee compared to women who drank no coffee (HR 1.81; 95% CI 1.10–2.95), which was interpreted as an approximately twofold higher risk than non-consumers of coffee, although no dose-response was statistically significant (*P* for trend 0.15). The EPIC prospective cohort study included 330,849 women, allowing the evaluation of coffee consumption and ovarian cancer risk [88]. During a median follow-up of 11.7 years, 1,244 women developed ovarian cancer. There was no significant association between coffee consumption and the risk of this malignancy when the top quintiles with no coffee intake were compared (HR 1.05; 95% CI 0.75–1.46), which was confirmed by the results of an updated meta-analysis performed by these researchers. Likewise, the recently published, well-documented meta-analysis by Wang et al. [71] of 9 prospective cohort studies indicated a summary RR of 1.04 (95% CI 0.90–1.20), which compared the highest versus lowest coffee intake and suggested no significant association, although regional differences between studies in the USA, Europe, and Canada were observed. The foregoing studies demonstrate inconsistent results for the association between coffee intake and ovarian cancer risk, although a recent meta-analysis suggests no significant association [89].

## Discussion

There is certainly evidence from experimental studies that coffee is able to counteract carcinogenesis. Investigations on potential modifiers for all-cause mortality in almost 4 million subjects have revealed that the lowest relative risk is present for cancer mortality for those who drink 2 cups per day (RR = 0.96; 95% CI 0.94–0.99, *p* < 0.0001) [90]. However, the significant amount of the lit-

erature on human studies on the relationship of coffee consumption with cancer risk suggests that coffee consumption may help reduce only hepatocellular cancer risk and possibly breast cancer risk [91, 92]. Nevertheless, a recent huge cohort study from the UK Biobank (46,155 cases and 270,342 controls) demonstrated that the relationship between coffee intake and individual cancer risks was consistent with a null effect [93]. Indeed, there are no conclusive results in case of esophageal, pancreatic, prostate, ovarian, colorectal, prostate, kidney, and bladder cancer. It should be noted however that although the coffee ingredient caffeine has been linked to unhealthy effects like increased serum lipid concentration, insulin resistance, and hypertension [94, 95], other coffee constituents are a major source of antioxidants. Studies using human cell lines have demonstrated an inhibitory effect of especially chlorogenic acids on various carcinogenic processes, including hepatocellular carcinogenesis [96]. Also, other proliferative processes have been shown to be inhibited by chlorogenic acids, which is reviewed and explained by Ludwig et al. [97] and Bohn et al. [98]. Potential mechanisms for these chemoprotective actions include the inhibition of oxidative stress, regulation of DNA repair, and apoptosis as well as inhibition of inflammation, neoangiogenesis, and proliferation.

A major point in the discussion on the pros and cons of coffee intake is whether the antioxidants and possible bioactive metabolites reach sufficient tissue concentration to be effective. Indeed, Clifford [99], in an eloquent article, states that only some 5% of dietary antioxidants are absorbed in the duodenum and of this, only some 5% reach the plasma unchanged. More than 95% of the antioxidant intake is fermented by the gut flora. Thus, the total concentration of bioactive compounds in plasma is very small, and this may explain the failure of epidemiologic studies to detect a favorable effect of dietary antioxidant intake, including coffee consumption. The effect of coffee is also notably influenced by the variations in caffeine and chlorogenic acids. Studies by Ludwig et al. [100] and Severini et al. [101] have emphasized that the caffeine and chlorogenic acid content in espresso coffee may vary. Roasting and coffee-making procedures differ in various coffee shops and countries. For instance, espresso coffee prepared in Italy contained 54–150 mg caffeine/serving, in Spain 82–139 mg/serving, and in Scotland 66–276 mg/serving. The content of chlorogenic acid varied from 20 to 81 mg/serving, from 92 to 188 mg/serving, and from 6 to 157 mg/serving, respectively. Generally, epidemiologic studies have not taken these local and geographical differences into account. It is evident



that these values have an effect on the plasma concentration and – most likely – the outcomes of human studies.

Besides this limitation, long-lasting questionnaire-based epidemiologic studies may suffer from other limitations, such as the fact that among the participants, noncancer mortality occurs as well. Also, self-reported coffee intake at recruitment may change for health reasons during the period of study. Other potential uncertainties that explain heterogeneity between studies include inhomogeneous patient sampling, different statistical analysis (deliberate), misreporting of socioeconomic status, education, coffee-brewing methods, cup size, temperature of coffee when drinking, caffeinated or decaffeinated coffee, smoking habits, and alcohol intake. Many of these often immeasurable factors, which may even change over lifetime before census, cause inconsistent outcomes among studies. Dietary antioxidant intake, sporting habits, and other lifestyle aspects may also influence outcomes on the association between coffee consumption and cancer risk [102]. Such methodological details in quoted investigations may explain the reported contradictions. As for future clinical population studies, efforts have been undertaken to develop guidelines in order to standardize health intervention studies [103]. Here, it is also important to mention that various types of cancer are difficult to detect at an early stage and that molecular approaches, especially those techniques that indicate genetic and epigenetic changes, may help the eye of the doctor [104]. Of special interest is the identification of oncometabolites which are associated with tumorigenesis [105]. These developments represent a future for “personalized cancer prevention” and may change epidemiologic results as mentioned in this article.

## Conclusion

All in all, our analysis of recent literature reveals that among coffee drinkers, there is a small reduction in the risk of hepatocellular cancer and possibly breast cancer.

## References

- 1 Hickman L. Product placement in the waiting room. *BMJ*. 2008;336(7656):1274–5.
- 2 Butt M, Sultan M. Coffee and its consumption: benefits and risks. *Crit Rev Food Sci Nutr*. 2011;51:363–73.
- 3 Erk T, Hauser J, Williamson G, Renouf M, Steiling H, Dionisi F, et al. Structure- and dose-absorption relationships of coffee polyphenols. *Biofactors*. 2014;40(1):103–12.
- 4 Spiller MA. The chemical components of coffee. *Prog Clin Biol Res*. 1984;158:91–147.
- 5 Gülçin İ. Antioxidant activity of food constituents: an overview. *Arch Toxicol*. 2012;86(3):345–91.
- 6 Liang N, Kitts DD. Antioxidant property of coffee components: assessment of methods that define mechanisms of action. *Molecules*. 2014;19(11):19180–208.
- 7 Priftis A, Stagos D, Konstantinopoulos K, Tsitsimpikou C, Spandidos DA, Tsatsakis AM, et al. Comparison of antioxidant activity between green and roasted coffee beans using molecular methods. *Mol Med Rep*. 2015;12(5):7293–302.
- 8 Cornelis MC, El-Sohemy A. Coffee, caffeine, and coronary heart disease. *Curr Opin Clin Nutr Metab Care*. 2007;10(6):745–51.

These effects are generally present at a moderate coffee intake of 2 cups/day. As to the risk of stomach and rectal cancer, recent studies indicate an elevated risk linked to coffee intake of 6.5 or more cups/day, especially evident in the US population. Although we found that coffee drinking does indeed contribute to the ingestion of antioxidant and anti-inflammatory bioactive compounds, a large part of the epidemiologic research demonstrates contrasting findings. This is obvious in case of esophageal, pancreatic, prostate, ovarian, colorectal, prostate, kidney, and bladder cancer. A large part of population studies suffers from factors which may even change over lifetime before census. Potential uncertainties arise from the self-reporting of socioeconomic status, education, sporting habits, quantity of coffee consumption, smoking habits, and alcohol intake. In addition, heterogeneity among studies includes inhomogeneous patient sampling (notably different lifestyle aspects) and different statistical analysis. These methodological and often untraceable factors may explain the reported contradictions.

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## Conflict of Interest Statement

The authors have no conflicts of interest to disclose.

## Author Contributions

E.K.J.P. conceived the structure of the manuscript and drafted the initial text. D.V. revised the original draft. Both authors approved the final manuscript.



- 9 McLellan TM, Caldwell JA, Lieberman HR. A review of caffeine's effects on cognitive, physical and occupational performance. *Neurosci Biobehav Rev.* 2016;71:294–312.
- 10 Perera V, Gross AS, McLachlan AJ. Measurement of CYP1A2 activity: a focus on caffeine as a probe. *Curr Drug Metab.* 2012;13(5):667–78.
- 11 Horrigan LA, Kelly JP, Connor TJ. Immunomodulatory effects of caffeine: friend or foe? *Pharmacol Ther.* 2006;111(3):877–92.
- 12 Muqaku B, Tahir A, Klepeisz P, Bileck A, Kreutz D, Mayer RL, et al. Coffee consumption modulates inflammatory processes in an individual fashion. *Mol Nutr Food Res.* 2016;60(12):2529–41.
- 13 Lang R, Dieminger N, Beusch A, Lee YM, Dunkel A, Suess B, et al. Bioappearance and pharmacokinetics of bioactives upon coffee consumption. *Anal Bioanal Chem.* 2013;405(26):8487–503.
- 14 Tao KS, Wang W, Wang L, Cao DY, Li YQ, Wu SX, et al. The multifaceted mechanisms for coffee's anti-tumorigenic effect on liver. *Med Hypotheses.* 2008;71(5):730–6.
- 15 Liang N, Kitts DD. Antioxidant property of coffee components: assessment of methods that define mechanisms of action. *Molecules.* 2014;19(11):19180–208.
- 16 Gaasht F, Dicato M, Diederick M. Coffee provides a natural multitarget pharmacopeia against the hallmarks of cancer. *Genes Nutr.* 2015;10:51.
- 17 Moeenfard M, Cortez A, Machado V, Costa R, Luis C, Coelho P, et al. Anti-angiogenic properties of cafestol and kahweol palmitate diterpene esters. *J Cell Biochem.* 2016;117(12):2748–56.
- 18 Bruno A, Pagani A, Pulze L, Albini A, Dallaglio K, Noonan DM, et al. Orchestration of angiogenesis by immune cells. *Front Oncol.* 2014;4:131.
- 19 Mišák M, Hoelzl C, Wagner KH. Impact of paper filtered coffee on oxidative DNA-damage: results of a clinical trial. *Mutat Res.* 2010;692:42–8.
- 20 Steinkellner H, Hoelzl C, Uhl M, Cavin C, Haidinger G, Gsur A, et al. Coffee consumption induces GSTP in plasma and protects lymphocytes against (+/-)-anti-benzo[a]pyrene-7,8-dihydrodiol-9,10-epoxide induced DNA- damage: results of controlled human intervention trials. *Mutat Res.* 2005;591:264–75.
- 21 Tresserra-Rimbau A, Medina-Remón A, Pérez-Jiménez J, Martínez-González MA, Casas MI, Corella D, et al. Dietary intake and major food sources of polyphenols in a Spanish population at high cardiovascular risk: the PREDIMED study. *Nutr Metab Cardiovasc Dis.* 2013;23(10):953.
- 22 Renouf M, Guy PA, Marmet C, Fraering AL, Longet K, Moulin J, et al. Measurement of caffeic and ferulic acid equivalents in plasma after coffee consumption: small intestine and colon are key sites for coffee metabolism. *Mol Nutr Food Res.* 2010;54(6):760–6.
- 23 Kang TY, Yang HR, Zhang J, Li D, Lin J, Wang L, et al. The studies of chlorogenic acid antitumor mechanism by gene chip detection: the immune pathway gene expression. *J Anal Methods Chem.* 2013;2013:617243.
- 24 Manach C, Scalbert A, Morand C, Rémésy C, Jiménez L. Polyphenols: food sources and bioavailability. *Am J Clin Nutr.* 2004;79(5):727–47.
- 25 Hirvonen T, Mennen LI, de Bree A, Castetbon K, Galan P, Bertrais S, et al. Consumption of antioxidant-rich beverages and risk for breast cancer in French women. *Ann Epidemiol.* 2006;16(7):503–8.
- 26 Fagherazzi G, Touillaud MS, Boutron-Ruault MC, Clavel-Chapelon F, Romieu I. No association between coffee, tea or caffeine consumption and breast cancer risk in a prospective cohort study. *Public Health Nutr.* 2011;14(7):1315–20.
- 27 Ganmaa D, Willett WC, Li TY. Coffee, tea, caffeine and risk of breast cancer: a 22-year follow-up. *Int J Cancer.* 2008;122:2071–6.
- 28 Bhoo-Pathy N, Peeters PH, Uiterwaal C, Bueno-de-Mesquita HB, Bulgiba AM, Bech BH, et al. Coffee and tea consumption and risk of pre- and postmenopausal breast cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort study. *Breast Cancer Res.* 2015 Jan 31;17(1):15.
- 29 Sanchez- Quesada C, Romanos- Nancrales A, Navarro A, Gea A, Cervantes S, Martínez-González MÁ, et al. Coffee consumption and breast cancer risk in the SUN project. *Eur J Nutr.* 2020;59(8):3461–71.
- 30 Jiang W, Wu Y, Jiang X. Coffee and caffeine intake and breast cancer risk: an updated dose-response meta-analysis of 37 published studies. *Gynecol Oncol.* 2013;129(3):620–9.
- 31 Gapstur S, Gaudet M, Wang Y, Hodge R, et al. *Cancer Epidemiol Biomarkers Prev.* 2020.
- 32 Tanaka K, Hara M, Sakamoto T, Higaki Y, Mizuta T, Eguchi Y, et al. Inverse association between coffee drinking and the risk of hepatocellular carcinoma: a case-control study in Japan. *Cancer Sci.* 2007;98(2):214–8.
- 33 Leung WW, Ho SC, Chan HL, Wong V, Yeo W, Mok TS. Moderate coffee consumption reduces the risk of hepatocellular carcinoma in hepatitis B chronic carriers: a case-control study. *J Epidemiol Community Health.* 2011;65(6):556–8.
- 34 Inoue M, Kurahashi N, Iwasaki M, Shimazu T, Tanaka Y, Mizokami M, et al. Effect of coffee and green tea consumption on the risk of liver cancer: cohort analysis by hepatitis virus infection status. *Cancer Epidemiol Biomarkers Prev.* 2009;18(6):1746–53.
- 35 Johnson S, Koh WP, Wang R, Govindarajan S, Yu MC, Yuan JM. Coffee consumption and reduced risk of hepatocellular carcinoma: findings from the Singapore Chinese Health Study. *Cancer Causes Control.* 2011;22(3):503–10.
- 36 Montella M, Polesel J, La Vecchia C, Dal Maso L, Crispo A, Crovatto M, et al. Coffee and tea consumption and risk of hepatocellular carcinoma in Italy. *Int J Cancer.* 2007;120(7):1555–9.
- 37 Hu G, Tuomilehto J, Pukkala E, Hakulinen T, Antikainen R, Vartiainen E, et al. Joint effects of coffee consumption and serum gamma-glutamyltransferase on the risk of liver cancer. *Hepatology.* 2008;48(1):129–36.
- 38 Yu C, Cao Q, Chen P, Tang, et al. An updated dose-response meta-analysis of coffee consumption and liver cancer risk. *Sci Rep.*
- 39 Bai K, Cai Q, Jiang Y, Lv L. Coffee consumption and risk of hepatocellular carcinoma: a meta-analysis of eleven epidemiological studies. *Oncol Targets Ther.* 2016;9:4369–75.
- 40 Zhao LG, Li ZY, Feng GS, Ji XW, Tan YT, Li HL, et al. Coffee drinking and cancer risk: an umbrella review of meta-analyses of observational studies. *BMC Cancer.* 2020;20(1):101.
- 41 Petrick JL, Freedman ND, Graubard BI, Sahasrabudhe VV, Lai GY, Alavanja MC, et al. Coffee consumption and risk of hepatocellular carcinoma and intrahepatic cholangiocarcinoma by sex: The Liver Cancer Pooling Project. *Cancer Epidemiol Biomarkers Prev.* 2015;24(9):1398–406.
- 42 Bhurwal A, Rattan P, Yoshitake S, Pioppo L, Reja D, Dellatore P, et al. Inverse association of coffee with liver cancer development: An updated systematic review and meta-analysis. *J Gastrointest Liver Dis.* 2020;29(3):421–8.
- 43 Naganuma T, Kuriyama S, Kakizaki M, Sone T, Nakaya N, Ohmori-Matsuda K, et al. Coffee consumption and the risk of oral, pharyngeal, and esophageal cancers in Japan: the Miyagi Cohort Study. *Am J Epidemiol.* 2008;168(12):1425–32.
- 44 Tverdal A, Hjellevik V, Selmer R. Coffee intake and oral-oesophageal cancer: follow-up of 389,624 Norwegian men and women 40–45 years. *Br J Cancer.* 2011;105(1):157–61.
- 45 Zamora-Ros R, Luján-Barroso L, Bueno-de-Mesquita HB, Dik VK, Boeing H, Steffen A, et al. Tea and coffee consumption and risk of esophageal cancer: the European prospective investigation into cancer and nutrition study. *Int J Cancer.* 2014;135(6):1470–9.
- 46 Zhang J, Zhou B, Hao C. Coffee consumption and risk of esophageal cancer incidence: a meta-analysis of epidemiologic studies. *Medicine.* 2018 Apr;97(17): e0514.
- 47 Hashibe M, Galeone C, Buys SS, Gren L, Boffetta P, Zhang ZF, et al. Coffee, tea, caffeine intake, and the risk of cancer in the PLCO cohort. *Br J Cancer.* 2015;113(5):809–16.
- 48 Xie Y, Huang S, He T, Su Y. Coffee consumption and risk of gastric cancer: an updated meta-analysis. *Asia Pac J Clin Nutr.* 2016;25(3):578–88.
- 49 Xie F, Wang D, Huang Z, Guo Y. Coffee consumption and risk of gastric cancer: a large updated meta-analysis of prospective studies. *Nutrients.* 2014;6(9):3734–46.
- 50 Li L, Gan Y, Wu C, Qu X, Sun G, Lu Z. Coffee consumption and the risk of gastric cancer: a meta-analysis of prospective cohort studies. *BMC* 2015;15:733.

- 51 Zeng SB, Weng H, Zhou M. Long-term coffee consumption and risk of gastric cancer: a PRISMA-compliant dose-response meta-analysis of prospective cohort studies. *Medicine (Baltimore)*. 2015 Sep;94(38):e1640.
- 52 Liu H, Hua Y, Zheng X, Shen C, Luo H, Tao X. Effect of coffee consumption on the risk of gastric cancer: a systematic review and meta-analysis of prospective cohort studies. *PLoS One*. 2015;10(5):e0128501.
- 53 Shen Z, Liu H, Cao H. Coffee consumption and risk of gastric cancer: an updated meta-analysis. *Clin Res Hepatol Gastroenterol*. 2015;39(2):245–53.
- 54 Deng W, Yang H, Wang J, Cai J, Bai Z, Song J, et al. Coffee consumption and the risk of incident gastric cancer: a meta-analysis of prospective cohort studies. *Nutr Cancer*. 2016;68(1):40.
- 55 Tran KT, Coleman HG, McMenamin ÚC, Cardwell CR. Coffee consumption by type and risk of digestive cancer: a large prospective cohort study. *Br J Cancer*. 2019;120(11):1059–66.
- 56 Guertin KA, Freedman ND, Loftfield E, Stolzenberg-Solomon RZ, Graubard BI, Sinha R. A prospective study of coffee intake and pancreatic cancer: results from the NIH-AARP Diet and Health Study. *Br J Cancer*. 2015;113(7):1081–5.
- 57 Bhoo-Pathy N, Uiterwaal C, Dik H, Jeurink S, Bech BH, Overvad K, et al. Intake of coffee, decaffeinated coffee, or tea does not affect risk for pancreatic cancer: results from the European Prospective Investigation into Nutrition and Cancer Study. *Clin Gastroenterol Hepatol*. 2013;11:1486–92.
- 58 Bidel S, Hu G, Jousilahti P, Pukkala E, Hakulinen T, Tuomilehto J. Coffee consumption and risk of gastric and pancreatic cancer: a prospective cohort study. *Int J Cancer*. 2013;132(7):1651–9.
- 59 Turati F, Galeone C, Edefonti V, Ferraroni M, Lagiou P, La Vecchia C, et al. A meta-analysis of coffee consumption and pancreatic cancer. *Ann Oncol*. 2012;23(2):311–8.
- 60 Wang A, Wang S, Zhu H. Coffee and cancer risk: A meta-analysis of prospective observational studies. *Sci Rep*. 2016 Sep 26;6:33711.
- 61 Isaksson B, Jonsson F, Pedersen NL, Larsson J, Feychting M, Permert J. Lifestyle factors and pancreatic cancer risk: a cohort study from the Swedish Twin Registry. *Int J Cancer*. 2002;98(3):480–2.
- 62 Sinha R, Cross AJ, Daniel CR, Graubard BI, Wu JW, Hollenbeck AR, et al. Caffeinated and decaffeinated coffee and tea intakes and risk of colorectal cancer in a large prospective study. *Am J Clin Nutr*. 2012;96(2):374.
- 63 Dominianni C, Huang WY, Berndt S, Hayes RB, Ahn J. Prospective study of the relationship between coffee and tea with colorectal cancer risk: the PLCO Cancer Screening Trial. *Br J Cancer*. 2013;109(5):1352–9.
- 64 Groessl E, Allison M, Larson J. Coffee consumption and the incidence of colorectal cancer in women. *J Cancer Epidemiol*. 2014;24:3708.
- 65 Yamada H, Kawado M, Aoyama N. JACC Study Group. Coffee consumption and risk of colorectal cancer: the Japan Collaborative Cohort Study. *J Epidemiol*. 2014;24:3708.
- 66 Schmit SL, Rennert HS, Rennert G, Gruber SB. Coffee consumption and the risk of colorectal cancer. *Cancer Epidemiol Biomarkers Prev*. 2016;25(4):634–9.
- 67 Je Y, Liu W, Giovannucci E. Coffee consumption and risk of colorectal cancer: a systematic review and meta-analysis of prospective cohort studies. *Int J Cancer*. 2009;124(7):1662–8.
- 68 Yu X, Bao Z, Zou J. Coffee consumption and risk of cancers: a meta-analysis of cohort studies. *BMC Cancer*. 2011;11:96.
- 69 Zhang X, Albanes D, Beeson W. Risk of colon cancer and coffee, tea, and sugar-sweetened soft drink intake: pooled analysis of prospective cohort studies. *J Natl Cancer Inst*. 2010;102:771–83.
- 70 Li G, Ma D, Zhang Y, Zheng W, Wang P. Coffee consumption and risk of colorectal cancer: a meta-analysis of observational studies. *Public Health Nutr*. 2013;16(2):346.
- 71 Wang A, Wang S, Zhu C, Huang U, Wu L, Wan X, et al. Coffee and cancer risk: a meta-analysis of prospective observational studies. *Sci Rep*. 2016 Sep 26;6:33711.
- 72 Micek A, Gnaiak A, Kawalec P, Brzostek T. Coffee consumption and colorectal cancer risk: a dose-response meta-analysis on prospective cohort studies. *Int J Food Sci Nutr*. 2013;64(10):1065–72.
- 73 Um C, McCullough M, Guinter M, Campbell P. Coffee consumption and risk of colorectal cancer in the Cancer Prevention Study-II Nutrition Cohort. *Cancer Epidemiol*. 2013;37(1):1–7.
- 74 Montella M, Tramacere I, Tavani A, Gallus S, Crispo A, Talamini R, et al. Coffee, decaffeinated coffee, tea intake, and risk of renal cell cancer. *Nutr Cancer*. 2009;61(1):76–80.
- 75 Lee JE, Hunter DJ, Spiegelman D, Adami HO, Bernstein L, van den Brandt PA, et al. Intakes of coffee, tea, milk, soda and juice and renal cell cancer in a pooled analysis of 13 prospective studies. *Int J Cancer*. 2007;121(10):2246.
- 76 Hu J, Mao Y, DesMeules M. Canadian Cancer Registries Epidemiology Research Group. Total fluid and specific beverage intake and risk of renal cell carcinoma in Canada. *Cancer Epidemiol*. 2009;33:355–62.
- 77 Huang TB, Guo ZF, Zhang XL, Zhang XP, Liu H, Geng J, et al. Coffee consumption and urologic cancer risk: a meta-analysis of cohort studies. *Int Urol Nephrol*. 2014;46(8):1481–93.
- 78 Ros MM, Bas Bueno-de-Mesquita HB, Büchner FL, Aben KK, Kampman E, Egevad L, et al. Fluid intake and the risk of urothelial cell carcinomas in the European Prospective Investigation into Cancer and Nutrition (EPIC). *Int J Cancer*. 2011;128(11):2695–708.
- 79 Yu X, Bao Z, Zou J, Dong J. Coffee consumption and risk of cancers: a meta-analysis of cohort studies. *BMC Cancer*. 2011;11:96.
- 80 Zhou Y, Tian C, Jia C. A dose-response meta-analysis of coffee consumption and bladder cancer. *Prev Med*. 2012;55(1):14–22.
- 81 Discacciati A, Orsini N, Wolk A. Coffee consumption and risk of nonaggressive, aggressive and fatal prostate cancer: a dose-response meta-analysis. *Ann Oncol*. 2014;25(3):584–91.
- 82 Park C, Myung S, Kim T. Coffee consumption and risk of prostate cancer: meta-analysis of epidemiological studies. *BJU Int*. 2010;106:762–9.
- 83 Liu H, Hu GH, Wang XC, Tang F, et al. Coffee consumption and prostate cancer risk: a meta-analysis of cohort studies. *Nutr Cancer*. 2015;67:392–400.
- 84 Taylor AE, Martin RM, Geybels MS, Stanford JL, Shui I, Eeles R, et al. Investigating the possible causal role of coffee consumption with prostate cancer risk and progression using Mendelian randomization analysis. *Int J Cancer*. 2017;140(2):322–8.
- 85 Steevens J, Schouten LJ, Verhage BA, Goldbohm RA, van den Brandt PA. Tea and coffee drinking and ovarian cancer risk: results from the Netherlands Cohort Study and a meta-analysis. *Br J Cancer*. 2007;97(9):1291–4.
- 86 Silvera SA, Jain M, Howe GR, Miller AB, Rohan TE. Intake of coffee and tea and risk of ovarian cancer: a prospective cohort study. *Nutr Cancer*. 2007;58(1):22–7.
- 87 Lueth NA, Anderson KE, Harnack LJ, Fulkerson JA, Robien K. Coffee and caffeine intake and the risk of ovarian cancer: the Iowa Women's Health Study. *Cancer Causes Control*. 2008;19(10):1365–72.
- 88 Braem MG, Onland-Moret NC, Schouten LJ, Tjønneland A, Hansen L, Dahm CC, et al. Coffee and tea consumption and the risk of ovarian cancer: a prospective cohort study and updated meta-analysis. *Am J Clin Nutr*. 2012;95(5):1172–81.
- 89 Salari- Moghaddan A, Milajerdi A, Surkan P, Larjani B, Esmaillzadeh A. Caffeine, type of coffee and risk of ovarian cancer: a dose-response meta-analysis of prospective studies. *J Clin Endocrinol Metabol*. 2019;104:5349–59.
- 90 Kim Y, Je Y, Giovannucci E. Coffee consumption and all-cause and cause-specific mortality: a meta-analysis by potential modifiers. *Eur J Epidemiol*. 2019 Aug;34(8):731–52.
- 91 Arab L. Epidemiologic evidence on coffee and cancer. *Nutr Cancer*. 2010;62(3):271–83.
- 92 Nkondjock A, Ghadirian P. Diet quality and BRCA-associated breast cancer risk. *Breast Cancer Res Treat*. 2007;103(3):361–9.
- 93 Ong JS, Law MH, An J, Han X, Gharahkhani P, Whiteman DC, et al. Association between coffee consumption and overall risk of being diagnosed with or dying from cancer among >300,000 UK Biobank participants in a large-scale Mendelian randomization study. *Int J Epidemiol*. 2019;48(5):1447–56.
- 94 Guessous I, Eap C, Bochud M. Blood pressure in relation to coffee and caffeine consumption. *Curr Hypertens Rep*. 2014 Sep;16(9):468.

- 95 Godos J, Pluchinotta F, Marventano S. Coffee components and cardiovascular risk : beneficial and detrimental effects. *Int J Food Sci Nutr*. 2014;65:925–36.
- 96 Granado-Serrano AB, Martín MA, Izquierdo-Pulido M, Goya L, Bravo L, Ramos S, et al. Molecular mechanisms of (-)-epicatechin and chlorogenic acid on the regulation of the apoptotic and survival/proliferation pathways in a human hepatoma cell line. *J Agric Food Chem*. 2007;55(5):2020–7.
- 97 Ludwig IA, Clifford MN, Lean ME, Ashihara H, Crozier A. Coffee: biochemistry and potential impact on health. *Food Funct*. 2014;5(8):1695–717.
- 98 Bøhn SK, Blomhoff R, Paur I. Coffee and cancer risk, epidemiological evidence, and molecular mechanisms. *Mol Nutr Food Res*. 2014;58(5):915–30.
- 99 Clifford M. Diet-derived phenols in plasma and tissues and their implications for health. *Planta Med*. 2004;70(12):1103–14.
- 100 Ludwig IA, Mena P, Calani L, Cid C, Del Rio D, Lean ME, et al. Variations in caffeine and chlorogenic acid contents of coffees: what are we drinking?. *Food Funct*. 2014;5(8):1718–26.
- 101 Severini C, Derossi A, Fiore AG, De Pilli T, Alessandrino O, Del Mastro A. How the variance of some extraction variables may affect the quality of espresso coffees served in coffee shops. *J Sci Food Agric*. 2016;96(9):3023–31.
- 102 Maruca A, Catalano R, Bagetta D, Mesiti F, Ambrosio FA, Romeo I, et al. The Mediterranean Diet as source of bioactive compounds with multi-targeting anti-cancer profile. *Eur J Med Chem*. 2019;181:111579.
- 103 Borges Miglievaca C, Stein C, Colpani V, Munn Z, Falavigna M. Quality assessment of prevalence studies. *J Clin Epidemiol*. 2020;127:59–68.
- 104 Koklesova L, Liskova A, Samec M, Qaradakhli T, Zulli A, Smejkal K, et al. Genoprotective activities of plant natural substances in cancer and chemopreventive strategies in the context of 3P medicine. *EPMA J*. 2020;11(2):261–87.
- 105 Gerner C, Costigliola V, Golubnitschaja O. Multiomic patterns in body fluids: technological challenge with a great potential to implement the advanced paradigm of 3P medicine. *Mass Spec Rev*. 2020;39(5–6):442–51.