Coffee and Cancer

Overview

In 2016, the International Agency for Research on Cancer (IARC) reviewed all available research on coffee and cancer, including research published since its original review in 1991, and found no clear association between coffee intake and cancer at any body site and, in some cases, found evidence that coffee drinking is associated with a reduced occurrence of certain cancers[1]. IARC therefore classified coffee in Group 3, for agents "not classifiable as to carcinogenicity to humans".

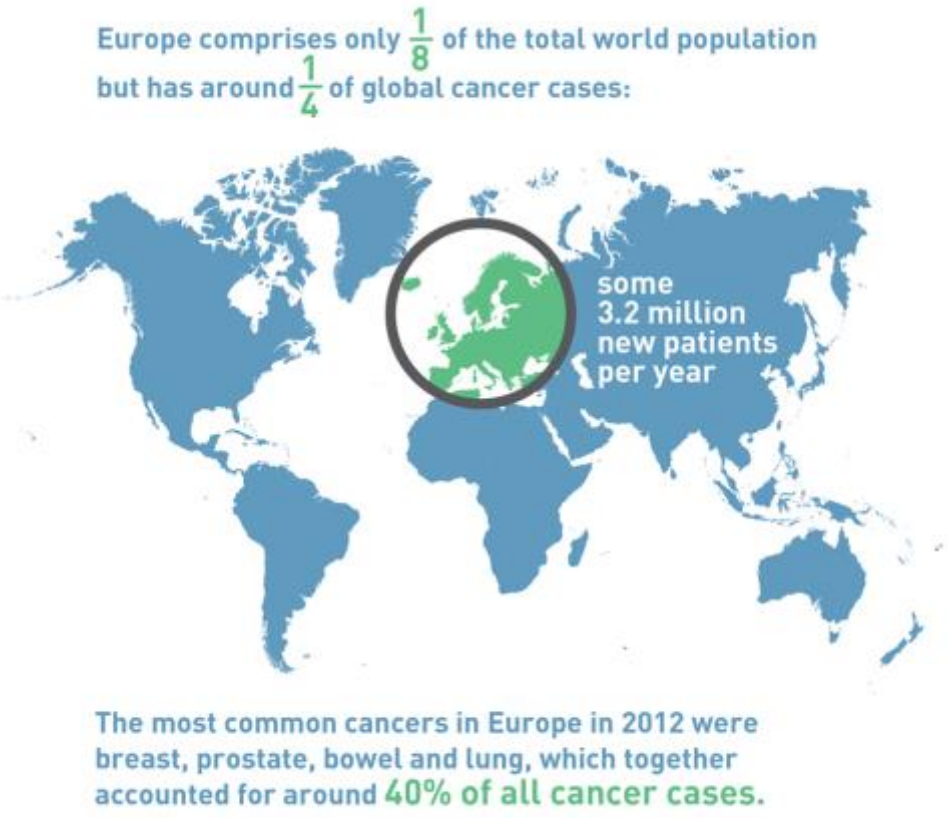
Specifically, IARC concluded that there is inadequate evidence to suggest any link between coffee consumption and cancer of the bladder, oral cavity, pharynx, lung, larynx, ovary, stomach, oesophagus, kidney or colorectum; or with childhood leukaemia[1]. Data suggests that there is no association between coffee consumption and increased risk of pancreas, breast and prostate cancers[1]. Research results also suggest that coffee drinking is associated with a reduced occurrence of cancers of the liver and uterine endometrium[1].

The body of scientific research suggests that, overall, moderate coffee drinking is not associated with an increased risk of developing cancer and in the case of certain cancers, may be associated with reduced risk. Moderate coffee consumption is typically defined as 3-5 cups per day, based on the European Food Safety Authority's review of caffeine safety[2].

Background Information

Cancer in Europe

According to data from the World Health Organization (WHO), cancer causes 20% of deaths in Europe[3]. With more than 3 million new cases and 1.7 million deaths each year, cancer is the most significant cause of death and morbidity in Europe after cardiovascular disease[3].



Europe comprises only one eighth of the total world population but has around one quarter of global cancer cases: some 3.2 million new patients per year[3]. The most common cancers in Europe in 2012 were breast, prostate, bowel and lung, which together accounted for around 40% of all cancer cases[4].

Coffee and cancer risk

In 2016, IARC included a large number of new studies in an updated review of the scientific research related to coffee and cancer. As a result of this review, IARC downgraded the classification of coffee from Group 2B to Group 3, for agents "not classifiable as to carcinogenicity to humans"[1]. IARC's 2016 review found no clear association between coffee intake and cancer at any body site. IARC's review also found that reduced risks were seen for cancers of the liver and uterine endometrium[1].

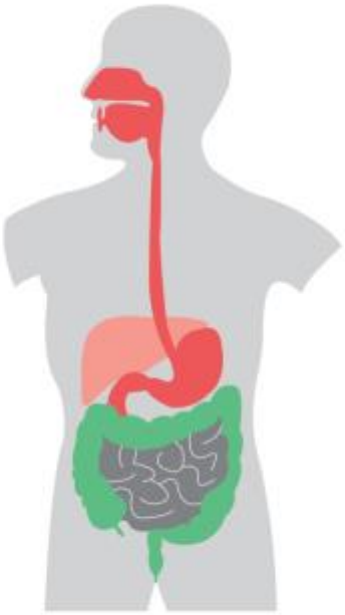
Comprehensive reviews of the data concerning coffee drinking and the risk of cancer at various sites have also been undertaken[5-12,13,14]. One, a 2011 meta-analysis of 40 prospective cohort studies, including over 2 million participants across Europe, North America and Asia, which assessed the association between coffee intake and cancer risk in humans quantitatively, found that coffee consumption was not associated with an increased risk of cancer[8]. A 2017 meta-analysis also concluded that coffee consumption

was not associated with overall cancer risk [13]. For some types of cancer, coffee intake was inversely associated with disease risk. A meta-analysis of observational studies published in 2016 concluded that coffee consumption was inversely associated with risk of oral, pharyngeal, colon, liver, prostate, and endometrial cancer risk and of risk of melanoma, but associated with an increased risk of lung cancer[14].A large Japanese cohort study also found no association between coffee consumption and increased risk of total cancer mortality[15].

In its *Scientific Opinion on the Safety of Caffeine*, published in 2015, The European Food Safety Authority concluded that: "caffeine intakes from all sources up to 400mg per day (about 5.7mg/kg bw per day for a 70kg adult) consumed throughout the day do not give rise to safety concerns for healthy adults in the general population. No health concerns in relation to acute toxicity, bone status, cardiovascular health, cancer risk or male fertility have been raised by other bodies in previous assessments for this level of habitual caffeine consumption and no new data have become available on these or other clinical outcomes which could justify modifying these conclusions"[2].

Coffee consumption and cancers of the digestive tract

[GRAPHIC: digestive tract]



Coffee and cancer of the oesophagus

Overall, research to date has not found an association between oesophageal cancer risk and the amount of coffee consumed.

- A literature survey pooled the data of 22 studies (17 case-control studies, 2 pooled analyses and 3 cohort studies; 14 originating from the USA and Europe), published between 1974 and 2008, looking at the relationship between the consumption of coffee and the risk of oesophageal cancer[16]. Most studies reported an unchanged, or reduced, risk of oesophageal cancer with the consumption of 3 or more cups of coffee per day. However, the majority of studies stated an increased risk with the increase in the temperature of hot drinks. There are, however, possible biases since the exact temperature of coffee, and the quantity and frequency of consumption, as well as the exact type of oesophageal cancer are unknown[16].
- A large meta-analysis published in 2011 found that coffee consumption was inversely associated with oesophageal cancer (relative risk 0.55)[8].
- In 2011, a further large Norwegian prospective study, of 389,624 middle-aged men and women followed up for over 14 years, found no relationship between coffee intake and cancer of the oesophagus[17].
- A 2013 meta-analysis of 7,376 oesophageal cancer cases concluded that both coffee and green tea, but not black tea, have protective effects on oesophageal cancer risk[18].
- The 2007 Second Expert Report by the World Cancer Research Fund (WCRF), a review of the worldwide evidence on food, nutrition, physical activity and 17 cancers, does not mention coffee in relation to oesophageal cancer[19].
- The 2016 IARC review concluded that the majority of the evidence shows no association between coffee consumption and oesophageal cancer[1].

In 2016, IARC classified beverages consumed at very high temperatures (defined as over 65°C) in Group 2A: "probably carcinogenic to the human oesophagus"[1]. 65°C is significantly hotter than the temperature at which most people can comfortably drink coffee without scalding their mouth and tongue[111,112]; coffee is typically drunk at temperatures below 60°C.

When IARC assessed evidence for a link between oesophageal cancer and coffee specifically, it found insufficient evidence of an association.

Coffee and stomach cancer

A series of meta-analyses on associations between coffee consumption and risk of stomach cancer have shown variable results, with the majority suggesting that there is no association between coffee consumption and risk of stomach cancer.

- A systematic review and meta-analysis of 23 studies found no association between coffee consumption and the development of stomach cancer in either cohort (relative risk 1.02) or case-control studies (relative risk 0.97)[20].
- A 2014 meta-analysis concluded that coffee consumption is not associated with risk of gastric cancer, although the authors suggested that smoking may confound some positive results and needs further investigation[21].
- Of 5 meta-analyses published in 2015, two concluded that coffee was not associated with the risk of gastric cancer[22,23] and three suggested that coffee consumption was associated with the development of gastric cancer[24-26]. Some studies reported varying results in participants from the United States compared to Europeans and Asians as well as those followed up for 10 years or less[22], whilst others suggested that coffee consumption may be a risk factor for gastric cardia cancer[22,26](cancer occurring in the upper portion of the stomach); therefore further research is required to provide clarification.
- A 2016 meta-analysis of 22 studies concluded that coffee consumption was associated with a decreased risk of gastric cancer, showing a greater effect at higher coffee intakes (up to 3 – 4 cups per day)[27].
- The WCRF 2007 Second Expert Report lists coffee under 'Limited Evidence – No Conclusion' in relation to stomach cancer[19].
- In 2016, IARC concluded that there was inadequate evidence to suggest any association between coffee consumption and stomach cancer[1].

Coffee and cancer of the upper aero-digestive tract

Although some research has suggested an inverse association between coffee consumption and risk of oral cavity/pharynx cancers, the 2016 IARC review concluded that the current evidence is inadequate to suggest such an association[1].

- A systematic meta-analysis of observational studies, published between 1989 and 2009, reported a 36% reduced risk for cancers of the oral cavity/pharynx (relative risk 0.64) between highest (3-5 and more cups per day) versus lowest (up to 1 cup per day) coffee drinkers, based on a total of 2,633 cases from one cohort and 8 case-control studies. On the other hand, there was no relation between coffee consumption and laryngeal cancer. There was no significant heterogeneity across studies[28].
- 2 meta-analyses found that coffee consumption was inversely associated with buccal and pharyngeal cancer (relative risk 0.49)[8,29].
- Additionally, a large Norwegian prospective study, of 389,624 middle-aged men and women followed up for over 14 years, also found no relationship between the amount of coffee consumed and the risk of cancer of the buccal cavity and pharynx; however, the authors could not exclude a weak inverse association[17].
- 2 meta-analyses in 2014 reviewing associations between coffee consumption and laryngeal cancers give conflicting results, one suggesting that tea and coffee

consumption was not associated with laryngeal cancers [30], whilst the other suggests coffee consumption, but not tea consumption, is associated with an increased risk[31].

- The WCRF 2007 Second Expert Report lists coffee under 'Limited Evidence – No Conclusion' for mouth, pharyngeal and laryngeal cancer[19].
- In 2016, IARC stated that although some research may suggest an inverse association, research results do vary and no conclusions can therefore be drawn[1].

Coffee and liver cancer

Liver cancer is the fifth most prevalent type of cancer worldwide, and the fourteenth most prevalent in Europe[4]. Studies looking at the relationship between coffee consumption and risk of liver cancer have found an inverse association, a conclusion also reached by IARC in its 2016 review[1].

- 5 meta-analyses reported a significant reduction in the risk of developing liver cancer[32-36]. One of these meta-analyses suggested a 40% reduction in risk of hepatocellular cancer for any coffee consumption compared to no coffee consumption[35]. Results from a 2015 multicentre prospective European cohort study further strengthened the existing research regarding the inverse association between coffee/tea and a reduced risk of hepatocellular cancer[37]. A 2016 dose response meta-analysis of prospective cohort studies suggested a linear association between coffee consumption and a reduced risk of liver cancer, also concluding that coffee drinking is inversely associated with liver cancer risk[38].
- In addition, a case-control study in Hong Kong among chronic hepatitis B virus carriers (a group at higher risk of developing liver cancer) found that moderate coffee drinkers, who drank coffee 4 times a week or more, had a 59% lower risk of developing liver cancer than non-coffee drinkers. There was also a significant dose-response effect[39]. Further work has suggested that the risk of evolution of hepatitis C to cancer was found to be reduced by 22% for each cup of coffee consumed, and for at least 3 cups daily the risk of disease progression is reduced by 62%[40].
- A study published in 2015 investigated the association between liver cancer and biological markers, concluding that the inverse association of coffee intake with hepatocellular cancer risk was partly accounted for by biomarkers of inflammation and hepatocellular injury[41]. In addition, the WCRF 2015 Liver Cancer Report lists coffee under a probable decrease in risk[42].
- In its 2016 review, IARC concluded that the evidence shows a consistent and statistically significant inverse association between coffee consumption and liver cancer[1].

There are two proposed mechanisms for coffee's association with a reduced risk of developing liver cancer and slower progression of liver disease[6,7,33,37].

- Cirrhosis is a major risk factor for the development of liver cancer and coffee has been shown to inhibit the elevation of hepatic transaminases, markers of hepatic disease[6,7,33].

- Coffee could reduce the circulating level of iron, and hence reduce the risk of hepatic carcinogenesis[39].

The role of antioxidants and other coffee components also warrant further investigation.

Coffee and cancer of the pancreas

Scientific research does not support an association between coffee consumption and an increased risk of pancreatic cancer. Indeed some, but not all, studies suggest an inverse association.

- A large Japanese cohort study, involving 102,137 participants followed over 11 years, did not observe an increased risk with coffee consumption[43]. The study even reported a reduced risk in men consuming 3 cups of coffee daily compared to non-coffee drinkers.
- A further meta-analysis, which included 14 cohort studies looking at coffee consumption and risk of pancreatic cancer, found a significant inverse relationship (relative risk 0.82)[8].
- Another meta-analysis of 14 cohort studies, covering Europe, the United States and Japan and including 671,080 individuals (1,496 cancer events) followed up for over 14 years, also identified an inverse association between coffee drinking and risk of pancreatic cancer in men[44]. Regular coffee drinkers had an 18% lower risk of cancer than non-drinkers; low to moderate coffee drinkers had a 14% lower risk; and high coffee drinkers had a 32% lower risk. Overall, an additional cup of coffee per day was associated with a 4% lower risk of pancreatic cancer.
- A further meta-analysis of 37 case-control and 17 cohort studies with 10,594 cases of pancreatic cancer showed that, overall, coffee consumption was not convincingly related to pancreatic cancer risk once smoking was taken into account, even at high intakes[45].
- In addition, a pooled-analysis of two Italian case-control studies found no association between the quantity of coffee consumed, the duration of exposure, and pancreatic cancer risk. These studies suggested that there was no causal association between coffee and pancreatic cancer[46].
- The WCRF 2012 Pancreatic Cancer Report lists coffee under 'Substantial Effect on Risk Unlikely'[47].
- IARC's 2016 review stated that cohort and population-based case-control studies together showed no association between coffee consumption and pancreatic cancer[1].

Coffee and colorectal cancer

A series of meta-analyses have been undertaken on coffee consumption and colorectal cancer risk, some of which suggest an inverse association.

- A 2004 meta-analysis on coffee and colorectal cancer included 3 cohort and 15 case-control studies from Japan, 8 European countries, Argentina and the USA, and

included 8,713 cases of cancer occurring in 147,227 subjects[48]. The authors reported heterogeneity linked to the design of the studies. Cohort studies did not observe any association, while case-control studies did generally find a relative risk below 1.

- Another meta-analysis of 5 cohort and 12 case-control studies, including 6,192 cases of colorectal cancer, found a 24% lower risk (relative risk 0.76) in those with a high coffee consumption (at least 4 cups/day) compared to non-coffee drinkers[49]. However a further meta-analysis concluded that whilst there was no observed protective effect on colorectal cancer of coffee consumption, there was no adverse effect either[50].
- A 2010 meta-analysis, including 24 case-control studies, reported a risk reduction of 17% in coffee drinkers compared to non-coffee drinkers, with risk falling by 6% for each cup of coffee consumed, and a 30% lower risk (relative risk 0.70) of colorectal cancer in the highest consumers[51].
- A further meta-analysis, including 15 cohort studies looking at coffee consumption and colorectal cancer, found an inverse association between coffee intake and the risk of colorectal cancer[8], a conclusion also found by a 2012 meta-analysis of observational studies including 15,522 cases, which suggested that coffee consumption could significantly decrease the risks of colorectal cancer and colon cancer, especially in Europeans and females[52].
- Two Japanese cohort studies, including 31,550 and 96,000 subjects respectively, reported a risk reduction of 56% with 3 or more cups per day, but only in women[53,54].
- A population-based study in northern Israel of 5,145 cases and 4,097 controls from the Molecular Epidemiology of Colorectal Cancer (MECC) study concluded that coffee consumption was associated with a 26% lower risk of developing colorectal cancer[55].
- The WCRF 2011 Colon and Rectum Report does not mention coffee as a risk factor[56].
- IARC's 2016 review concluded that most informative cohort studies show no association between coffee consumption and increased risk of colorectal cancer[1].

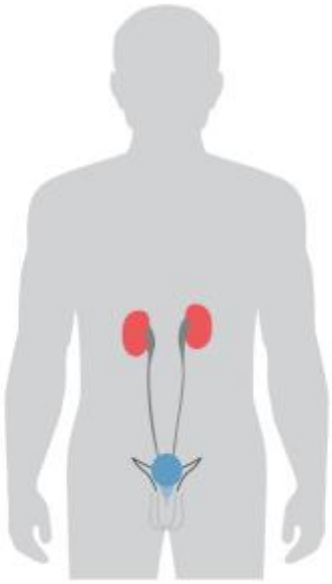
Only one meta-analysis shows a dose-response relationship[46], which suggests either a threshold effect or a difference between coffee drinkers and non-coffee drinkers. It could potentially represent a confounding factor linked to the decrease in coffee consumption in patients after the onset of symptoms.

The inverse association between coffee consumption and colorectal cancer risk has been attributed to a number of factors[48-51,57], including:

- The anti-carcinogenic properties of coffee diterpenes and antioxidants[48-51].
- Coffee's capacity to induce the excretion of biliary acids and neutral sterols in the colon[48-51].
- The stimulation of colon motility, reducing the length of time mutagens are in contact with the intestinal mucosa[48-51].
- Caffeine's inhibition of colon cancer cell growth[57].

Coffee consumption and bladder, kidney and prostate cancers

[GRAPHIC: bladder, kidney and prostate]



Coffee and bladder cancer

Early, limited research had suggested a potential association between coffee and bladder cancer. However, more recent studies have provided sufficient evidence for IARC to conclude that there is inadequate evidence of such an association, highlighting that smoking may have confounded results in some earlier studies[1].

- 7 meta-analyses have reviewed the associations between coffee consumption and bladder cancer risk, presenting variable result [58-64]. Based on current research it is difficult to draw firm conclusions about associations between coffee consumption and bladder cancer risk.
- Some papers report an increased risk of bladder cancer[58,64] including a 2001 meta-analysis, which concluded that coffee consumption increased the risk of urinary tract cancer by 20%[59]. However, other analyses did not find a clear association[60-64]. A 2017 study, following 73,346 Japanese individuals where 274 cases of bladder cancer were identified, concluded that the data indicates a significant inverse association between coffee consumption and bladder cancer[65].
- A number of confounding factors have been reported, including smoking, maleness and Asian origin. 3 meta-analyses suggest that compared with smokers, non-smokers appear to have a slightly increased risk of bladder cancer[58,63,64], although a 2017 Japanese study concluded that an inverse association between coffee consumption and bladder cancer was observed even when stratified for smoking

status[65]. Further data suggests that coffee consumption is associated with a decreased risk of bladder cancer in Asian people[63]. Some research also suggests an increased risk of bladder cancer in male coffee drinkers[65,66]. Further work is required to understand these associations in more detail.

- Research investigating a dose response relationship between coffee intake and bladder cancer is also limited. A 2014 meta-analysis found no association between coffee consumption and bladder cancer, but since the authors reported insignificant associations in analysis of intakes (highest vs. none/lowest) and in dose response analyses, further research is again required[63].
- The WCRF 2015 Bladder Cancer Report lists coffee under 'Limited Evidence – No Conclusion'[67].
- IARC's 2016 review found no clear association between coffee intake and cancer at any body site, including the bladder. Residual confounding factors, particularly smoking, were highlighted as factors that may have distorted results in some earlier bladder cancer studies[1].

Coffee and kidney cancer

Research consistently suggests there is no conclusive link between coffee consumption and kidney cancer.

- During the last three decades, the incidence of kidney cancer has constantly increased, leading to the search for possible links with diet. The etiology of kidney cancer suggests an increased risk with smoking and being overweight[68].
- The World Cancer Research Fund (WCRF) identified 18 case-control and 5 cohort studies indicating the lack of a link between coffee consumption and kidney cancer[19].
- A few additional studies reviewed, including a synthesis of 13 prospective studies including 530,469 women, 244,483 men and 1,478 cases of kidney cancer, did not find an association between coffee consumption and kidney cancer (relative risk 0.99 – mean for all studies)[68,69], and a 2014 meta-analysis also found no association[63].
- The WCRF 2015 Kidney Cancer Report lists coffee under 'Limited Evidence – No Conclusion'[70].
- In 2016, IARC concluded that there is inadequate evidence to suggest any association between coffee consumption and kidney cancer[1].

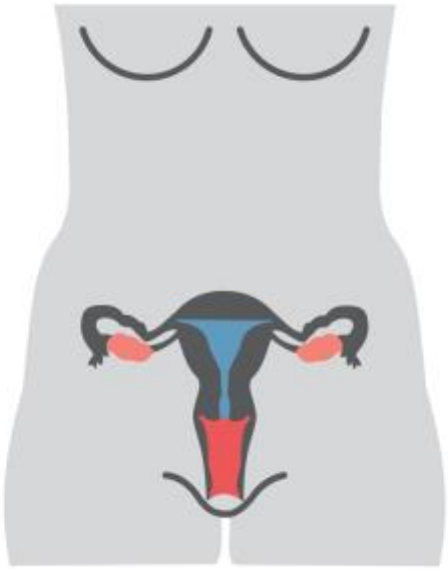
Coffee and prostate cancer

Research suggests that coffee consumption is not associated with an increased risk of prostate cancer.

- A meta-analysis of 6 cohort and 5 case-control studies found no influence of coffee consumption on the risk of developing prostate cancer[71]. Coffee consumption cumulated over the entire lifespan, age of onset and duration had no effect on the incidence of prostate cancer.

- However, a 2011 meta-analysis found that coffee drinkers had a 21% lower risk of developing prostate cancer than non-coffee drinkers (relative risk 0.79)[8].
- A prospective analysis of 47,911 men in the Health Professionals Follow-up Study, 5,035 of which had prostate cancer, observed a strong inverse association between coffee consumption and risk of advanced prostate cancer. Men who consumed 6 or more cups of coffee per day had a 60% lower risk of lethal and advanced prostate cancer than non-drinkers. The association appeared to be related to the non-caffeine components of coffee, as the association with lethal cancer was similar for regular and decaffeinated coffee[72].
- A 2014 meta-analysis suggested that coffee consumption has a protective effect on prostate cancer, concluding that coffee consumption may be inversely associated with the risk of fatal prostate cancer, but showed no clear evidence of an association with its incidence[73].
- 3 further meta-analyses published in 2014 also supported the hypothesis that coffee consumption may decrease the risk of prostate cancer[74-76]. One suggested a significant inverse relationship for fatal prostate cancers and high-grade prostate cancers[74], whilst a second suggested that intakes of coffee greater than 4 or 5 cups per day may be associated with a reduced risk of overall prostate cancer, as well as fatal and high-grade prostate cancers[75].
- A 2015 meta-analysis concluded that coffee consumption may be associated with a reduced risk of prostate cancer, particularly amongst European populations, and observed an inverse association with non-advanced prostate cancer[77].
- The WCRF 2015 Prostate Cancer Report lists coffee under 'Limited Evidence – No Conclusion'[78].
- IARC's 2016 review concluded that research consistently suggests no association between coffee consumption and risk of prostate cancer[1].

Coffee consumption and breast, ovary and endometrial cancers



Coffee and breast cancer

Research to date has not linked coffee consumption to an increased risk of breast cancer overall. Data in pre-menopausal women who are regular coffee drinkers suggests there may be a protective effect.

- One meta-analysis found that coffee drinking was inversely associated with breast cancer risk (relative risk 0.94)[8].
- The results of a French prospective study, which followed 67,703 women for 11 years, showed no relationship between coffee or caffeine intake and breast cancer risk overall[79].
- The WCRF 2010 Breast Cancer Report does not mention coffee as a risk factor[80].
- IARC's 2016 review concluded that studies show either no association, or a modest inverse association, between breast cancer risk and coffee consumption[1].

Post-menopausal women

Studies have shown no association between coffee consumption and the incidence of breast cancer in post-menopausal women.

- The main studies include large samples from French, Italian and Swedish populations followed up for 6-10 years[6-8].
- A meta-analysis of 9 cohort and 9 case-control studies suggested that increasing coffee consumption by 2 cups daily tended to reduce the risk of breast cancer[81]. However, the results showed a borderline significant association between coffee consumption and reduced risk of breast cancer in the United States and Europe, but not in Asia. This difference may originate in the limited sample size of studies conducted in Asia. Furthermore, coffee consumption did not appear to be associated

with an altered risk of benign breast disease and subsequent development of breast cancer.

- In addition, a large Dutch study found no association between coffee and the risk of breast cancer across all levels of intake, and no link with either lifestyle or body mass index (BMI)[82].
- A Swedish study of 5,929 women (2,818 cases and 3,111 controls) showed a significantly lower risk of non-hormone receptive breast cancer in heavy coffee drinkers (more than 5 cups a day) compared to those who drank less than 1 cup a day[83].
- 2 further meta-analyses were published in 2013 [84,85]: one suggested that coffee/caffeine intake might be weakly associated with breast cancer risk for post-menopausal women (59,018 breast cancer cases, 966,263 participants)[84]. The second (49,497 cases) concluded that increased coffee intake is not associated with a significantly reduced risk of breast cancer, but reported an inverse association in oestrogen receptor negative cases[85].

Pre-menopausal women

In pre-menopausal women, the consumption of regular coffee (4 cups a day) has been associated with a 38% lower risk of breast cancer (relative risk 0.62)[6].

- In pre-menopausal women who carry the BRCA1 and BRCA2 mutation, a 2006 study suggested that the risk of breast cancer is reduced by 25-70% with daily consumption of 4-6 cups of coffee, compared to non-coffee drinkers. However, this effect is limited to regular coffee; it is not observed with decaffeinated coffee[86]. In contrast, a 2013 study reported a significant association between coffee consumption and breast cancer risk for BRCA1 mutation carriers[84].
- The risk of breast cancer is also modulated by the CYP1A2 gene, and the interaction between coffee consumption and the polymorphisms A and C of this gene have been studied. Women carrying at least one C allele (AC or CC), who consume coffee, have a 64% reduced risk compared to non-coffee drinkers. Coffee has not been shown to have an effect in women with the AA genotype[87].

Clearly further research is required to clarify the detail in this area, and integrating individual genetic variability when assessing diet-disease associations is likely to be important.

Coffee and ovarian cancer

Ovarian cancer is the fifth most common and lethal cancer in women in Europe[4]. Research to date has shown no conclusive association between coffee consumption and risk of ovarian cancer.

- A meta-analysis of 8 well controlled case-control studies and 3 prospective cohort studies found that coffee consumption did not have an effect on the development of ovarian cancer[88].
- A 2012 meta-analysis based on data from all women taking part in the European Prospective Investigation into Cancer and Nutrition (EPIC) also concluded that the studies reviewed by the authors do not provide sufficient research to support an association between coffee and tea consumption and risk of ovarian cancer[89].
- The WCRF 2014 Ovarian Cancer Report lists coffee under 'Limited Evidence – No Conclusion'[90].
- IARC's 2016 review concluded that there is inadequate evidence to suggest an association between coffee consumption and ovarian cancer[1].

Coffee and endometrial cancer

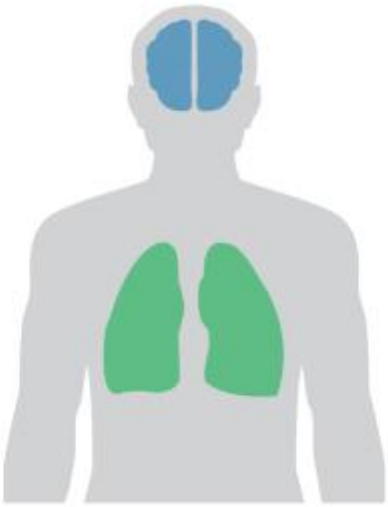
The majority of data available suggests that coffee consumption is linked to a lower risk of endometrial cancer. IARC's 2016 review found that many epidemiological studies showed reduced risks for cancers of the uterine endometrium[1].

- A meta-analysis, including 2 cohort (201 cases) and 7 case-control studies (2,409 cases), showed that coffee drinkers were 20% less likely to develop endometrial cancer than non-coffee drinkers (relative risk 0.80), but there was significant heterogeneity between the studies[91]. Compared with non-drinkers, low-to-moderate coffee drinkers (1-4 cups per day) had a 13% lower risk (relative risk 0.87) of endometrial cancer and heavy drinkers (more than 4 cups per day) had a 36% lower risk (relative risk 0.64). The risk was reduced by 7% for each additional cup of coffee per day. The data suggests an inverse relationship between coffee and endometrial cancer but the causality is unclear.
- 3 later studies not included in the above meta-analysis also concluded a dose-dependent effect of coffee consumption on reduced risk of endometrial cancer. In American women, those who drank more than 2 cups of coffee a day had a 29-35% lower risk of developing endometrial cancer than non-coffee drinkers[92,93]. Overweight Swedish women who drank coffee also had a lower risk of endometrial cancer[94].
- A further meta-analysis found a 26% reduction in the risk of endometrial cancer among coffee drinkers, compared with non-drinkers, and a reduction in risk of over 30% among heavy coffee drinkers[8].
- A 2012 meta-analysis including 6,628 endometrial cancer cases suggests that increased coffee intake is associated with a reduced risk of endometrial cancer, consistently observed for cohort and case-control studies[95].
- One of the meta-analyses published in 2015 supported earlier findings that coffee and caffeine intake might significantly reduce the incidence of endometrial cancer. The inverse association between coffee intake and endometrial cancer incidence was more pronounced in patients who were never treated with hormones and subjects with a body mass index >25kg/m^2 [96]. A second meta-analysis suggested a weak association for coffee consumption, but the authors acknowledged that there may

have been selective publication of only part of the research in some of the prospective studies[97].

- The WCRF 2013 Endometrial Cancer Report lists coffee under a probable decrease in risk, and mentions that the effect is found in both caffeinated and decaffeinated coffee and cannot be attributed to caffeine[98].
- IARC's 2016 review concluded that the scientific research showed an inverse association between coffee consumption and risk of developing endometrial cancer[1].

Coffee consumption and cancers at other sites



Coffee and skin cancer

There is no research to currently suggest that coffee consumption is linked to skin cancer. Caffeine, however, may protect skin cells against the harmful effects of UVB radiation[99-103].

- In 2008, a study in mice reported that caffeine added to drinking water, or placed directly onto the skin, induced the death of cells damaged by UVB irradiation. In 2009, the same work performed on human skin cell cultures showed that caffeine doubled the mortality of the cells damaged by UVBs, hence decreasing the risk of cancer[99].
- The underlying molecular mechanism is similar in both species, which led the authors to hypothesize that caffeine, or a substance with a similar mode of action, could protect human skin from the deleterious action of UVBs when applied topically[100].

The WCRF 2007 Second Expert Report lists coffee under 'Limited Evidence – No Conclusion' for skin cancer[19]. However, a 2015 systematic review and meta-analysis concluded that there is a possible association between regular coffee consumption and a reduced risk of melanoma, although the authors suggest further research is required[101].

Two further studies have investigated a dose response effect. A 2015 publication suggested that cutaneous melanoma risk decreased by 3% and 4% for a 1 cup increment of total coffee and caffeinated coffee, respectively[102]. A subsequent 2016 paper concluded that a linear dose response effect was observed between a reduced risk of malignant melanoma and caffeinated coffee consumption, but not decaffeinated coffee[103].

Coffee and lung cancer

Although a high consumption of coffee (more than 5 cups per day) has been associated with an increased risk of lung cancer, residual confounding effects of smoking or other factors have been identified by IARC[(1).]

- A 2010 meta-analysis, including 5 prospective and 8 case-control studies involving 5,347 lung cancer cases and 104,911 non-cases, reported an association between the highest coffee intake (at least 5-7 cups a day) and lung cancer, i.e. those who consumed the most coffee had a 27% higher risk of developing lung cancer (relative risk 1.27). The increase in coffee consumption of 2 cups per day led to a 14% increased risk for lung cancer (relative risk 1.14)[104].
- The highest coffee consumption was significantly associated with increased risk of lung cancer in prospective studies, and studies conducted in America and Japan, but borderline significantly associated with decreased risk of lung cancer in non-smokers[104].
- A 2016 meta-analysis of 12,276 cases of lung cancer and 102,516 controls suggested a significant association between intake of 3 or more cups of coffee per day and increased risk of lung cancer in men but not in women, in American and Asian populations but not in European populations, and in smokers but not non-smokers[105].
- The WCRF 2007 Second Expert Report lists coffee under 'Limited Evidence – No Conclusion' for lung cancer[19].
- IARC's 2016 review stated that although a positive association is observed in some studies, this is most likely to be explained by confounding factors such as smoking. The report concluded that there was inadequate evidence to suggest any association between lung cancer and coffee consumption[1].

Coffee and brain tumours

Coffee consumption may be linked to a reduced risk of brain tumours, in men in particular, but given that the number of studies is limited, more research is required to confirm this inverse association.

- The data from a synthesis of 3 cohort studies conducted in the USA, including 335 cases, showed that the consumption of at least 5 cups of coffee and tea daily, compared with no tea or coffee, was associated with a 40% lower risk of glioma

(relative risk 0.60)[106]. No association was observed between decaffeinated coffee and glioma risk. Among women, the significant inverse association observed was weaker than among men.

- A European study of 343 cases of newly diagnosed glioma in nine countries showed the same results, i.e. a significant 34% lower risk of glioma among subjects consuming over 100ml (1 cup) coffee and tea per day compared with those consuming less than 100 ml/day (relative risk 0.66)[107]. In this study, the association was also slightly stronger in men than in women.
- The WCRF 2007 Second Expert Report does not mention coffee in relation to cancers of the nervous system (including brain tumours)[19]. Similarly, IARC has not reviewed coffee consumption in relation to brain tumours[1].

Maternal coffee consumption and childhood leukemia

There are limited studies in this area with some variable results, but IARC concluded that the research was not conclusive enough to suggest any associations. Pregnant and breastfeeding women are advised by EFSA to drink no more than 200mg of caffeine per day from all sources, which is equivalent to 2-3 cups of coffee[2].

- Authors of a 2015 meta-analysis comprising a total of 3,649 cases and 5,705 controls conclude that their findings "confirm the detrimental association between maternal coffee consumption and childhood leukemia risk, and provide indications for a similar role for maternal cola consumption"[108].
- A further study published in 2015 examining parental smoking, maternal alcohol, coffee and tea consumption during pregnancy, and childhood acute leukemia concluded that childhood acute leukemia was not associated with coffee consumption during pregnancy, but an association was seen between coffee consumption and acute lymphoblastic leukemia[109].
- IARC's 2016 review concluded that a lack of consistency amongst studies led to inconclusive and inadequate evidence of any association between coffee consumption and childhood leukaemia[1].

Influence of the mode of coffee preparation

According to a Swedish study with 64,603 participants, including 3,034 cases – the first study to look at the influence of coffee preparation on cancer risk – the risk of cancer could vary between drinkers of filtered or boiled coffee[110]:

- For all sites combined, as well as for prostate and colon alone, there was no association between mode of coffee preparation and cancer risk.
- For breast cancer, 4 cups or more of boiled coffee per day compared to 1 or fewer decreased the risk by 48%.
- An increased risk was found in pre-menopausal and a decreased risk in post-menopausal women for total and filtered coffee, respectively.

- The consumption of boiled coffee increased the risk of pancreatic cancer in both sexes, and of cancer of the respiratory tract in men.
- IARC also stated that "studies that have been reported do not show consistent and robust differences in cancer risk for different kinds of coffee or different preparation methods"[1].

Influence of the temperature of hot beverages

In 2016, IARC classified beverages consumed at very high temperatures (defined as over 65°C) in Group 2A: "probably carcinogenic to the human oesophagus"[1]. 65°C is significantly hotter than the temperature at which most people can comfortably drink coffee without scalding their mouth and tongue[111,112]; coffee is typically drunk at temperatures below 60°C. When IARC assessed evidence for a link between oesophageal cancer and coffee specifically, it found insufficient evidence of an association.

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