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ORIGINAL ARTICLE

Coffee consumption, cancer, and healthy aging: epidemiological evidence and underlying mechanisms

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Abstract This comprehensive review examines the role of coffee consumption in promoting healthy aging and its potential impact on cancer prevention. Previous research has shown that moderate coffee intake may contribute to extending healthspan and enhancing longevity through beneficial effects on cardiometabolic health and key biological processes involved in aging. However, the relationship between coffee consumption and cancer risk remains controversial. This review synthesizes longitudinal observational and interventional data on the effects of coffee consumption on overall and site-specific cancers, explores underlying biological mechanisms, and discusses clinical and public health implications. Additionally, the review highlights evidence from Mendelian randomization (MR) studies to assess potential causal relationships. Our findings suggest that coffee consumption is associated with a reduced risk of several cancers, including skin, liver, prostate, and endometrial cancers, and may also lower cancer recurrence rates, particularly in colorectal cancer. These protective associations appear consistent across different demographic groups, with the most significant benefits observed at consumption levels of three or more cups per day. However, evidence is inconclusive for many other cancers, and coffee consumption is consistently linked to an increased risk of lung cancer. MR studies generally do not support a strong causal relationship for most cancers, though some suggest potential protective effects for hepatocellular, colorectal, and possibly prostate cancers, with mixed results for ovarian cancer and an increased risk for esophageal cancer and multiple myeloma. The protective effect of coffee on liver and prostate cancer is supported by both observational and MR studies. The potential anti-cancer benefits of coffee are attributed to its bioactive compounds, such as caffeine, chlorogenic acids, and diterpenes, which possess antioxidant and anti-inflammatory properties. These compounds may reduce oxidative stress, inhibit cancer cell proliferation, induce apoptosis, and modulate hormone levels. The review emphasizes the need for

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further research to clarify dose–response relationships, causal associations, and the biological mechanisms underlying these associations. While coffee consumption appears to contribute to cancer prevention and healthy aging, caution is warranted due to the increased risk of certain cancers, highlighting the complexity of its health effects.

Keywords Coffee consumption · Caffeine · Cancer · Mortality · Healthspan · Longevity · Mendelian randomization

Introduction

Cancer remains one of the leading causes of morbidity and mortality worldwide, significantly impacting public health through its associated clinical burden, healthcare costs, and its adverse effects on the healthspan and longevity. Cancer is the second commonest global cause of death after ischemic heart disease [1]. There were an estimated 20 million new cancer cases and 9.7 million deaths in 2022 [2]. The incidence and mortality rates of cancer have profound implications, with incidence and survival rates varying significantly by cancer type and sex [2]. The epidemiology of cancer is complex, influenced by risk factors that range from genetic predispositions to lifestyle factors [3]. Modifiable lifestyle factors, including tobacco use, physical inactivity, unhealthy diets, harmful use of alcohol, and environmental factors, play critical roles in the development and progression of cancer [4]; in the USA, 40% of all cancers are associated with modifiable risk factors. Tobacco use is a major risk factor, contributing to lung cancer and other malignancies [5], while poor dietary habits and physical inactivity are linked to various cancers, including colorectal and breast cancer [6, 7].

Dietary factors are increasingly recognized for their role in modulating chronic disease outcomes, including cardiovascular diseases (CVDs) and cancer [8–10]. Diets rich in fruits, vegetables, whole grains, and lean proteins are associated with reduced risks of these conditions. Specific nutrients and dietary patterns have been shown to confer protective effects [10].

Coffee is one of the most widely consumed beverages in the Western world, playing a significant cultural and economic role in daily life. Globally, more than 10 million tons of coffee are produced each year, with the majority being consumed in Western countries where it is deeply integrated into social rituals and daily routines. In the USA alone, over 60% of adults drink coffee daily, contributing to the consumption of approximately 400 million cups per day [11]. This equates to over 146 billion cups annually, making the USA one of the largest consumers of coffee globally. Europe also holds a dominant position [12]. The ubiquity of coffee consumption in the Western world has sparked extensive research into its health implications, with a growing body of evidence suggesting that coffee is more than just a stimulant. Its potential impact on chronic age-related diseases has become a subject of considerable interest, as it could hold significant implications for public health strategies aimed at promoting healthy aging and reducing the burden of disease. Given the widespread consumption of coffee and its potential health benefits and risks, understanding its role in prevention of age-related diseases, particularly in relation to cancer, is of paramount importance. Our recent state-of-the-art review provides a history of the origins of coffee and its journey through medical scrutiny [13]. We have also highlighted the potential of moderate coffee consumption to extend healthspan and promote longevity through its beneficial effects on several adverse cardiometabolic outcomes [13]. These outcomes, such as CVD, type 2 diabetes, and metabolic syndrome, are closely linked to the aging process and are significant contributors to age-related diseases. By positively influencing these conditions, coffee consumption may play a critical role in reducing the burden of age-related diseases, thereby promoting a longer and healthier life [14–16].

Evidence suggests that coffee consumption might be linked with a reduced risk of overall cancer. However, the evidence has not been entirely consistent, especially across site-specific cancers. While some studies indicate a reduced risk of certain cancers, such as endometrial cancer [17], others suggest an increased risk for cancers like pancreatic or lung cancer [18, 19], or no association at all for cancers like ovarian or colorectal cancer [20, 21]. These discrepancies may be influenced by factors such as smoking status and body mass index (BMI). Furthermore, Mendelian randomization (MR) studies, which help determine causal relationships, have yielded mixed results regarding coffee consumption and cancer outcomes [22, 23]. It is uncertain

if coffee consumption can impact on healthspan and longevity via its effect on cancer outcomes. Given the substantial public health burden of cancer, it is relevant to synthesize the overall evidence on coffee consumption and cancer risk. This review aims to synthesize existing evidence from observational, interventional, and genetic studies on the impact of coffee consumption on both overall and site-specific cancers. It seeks to elucidate the biological mechanisms at play, explore the implications for healthspan and longevity, discuss clinical and policy implications, identify gaps in current knowledge, and propose directions for future research.

Methods

The search strategy involved a comprehensive review of MEDLINE and Embase databases up to August 2024. The focus was on observational longitudinal studies, including prospective cohort, nested case–control, case-cohort, and retrospective cohort studies, as well as interventional studies. We particularly emphasized on large prospective cohort studies as well as systematic reviews and meta-analyses, adhering to the established hierarchy of evidence [24]. Umbrella reviews of systematic reviews were also included. Keywords related to coffee consumption (e.g., "coffee," "caffeine") and various types of cancer (e.g., "cancer," "lung cancer," "colorectal cancer," "digestive cancer," "skin cancer," "prostate cancer," "cancer mortality," "cancer recurrence") were utilized in our search. We limited the review to studies conducted on human populations, published in English, and involving adult subjects. We extracted and reported multivariably adjusted risk estimates (odds ratios (ORs), relative risks (RRs) and hazard ratios (HRs)) for associations demonstrating significant effects. Cross-sectional studies were excluded as they do not address the issue of temporality. Individual case–control studies were not specifically evaluated, except for when their results were pooled with results of observational longitudinal studies. Additionally, to explore genetic associations between coffee consumption and cancer outcomes, we performed a separate search focusing on MR studies examining coffee or caffeine intake and cancer.

Bioactive components of coffee

Coffee is a complex beverage composed of over 100 biological and chemical components, many of which have significant bioactive properties. These bioactive components contribute to coffee's health benefits and include diterpenes, magnesium, trigonelline, quinides, lignans, alkaloids, and phenolic compounds [25]. Coffee contains diterpenes such as cafestol and kahweol, which have been shown to have anti-inflammatory and potential anti-cancer properties [26]. However, they can also raise cholesterol levels in some individuals [26]. Magnesium is an essential mineral present in coffee and contributes to numerous physiological functions, including muscle and nerve function, blood sugar control, and bone health. Trigonelline is an alkaloid found in coffee and has been associated with various health benefits, including potential anti-diabetic effects and neuroprotective properties [27]. Quinides are compounds formed during the roasting process that have been shown to improve glucose metabolism and insulin sensitivity [28]. Lignans are polyphenolic compounds that have antioxidant properties and are linked to reduced risks of CVDs and certain types of cancer [29]. Besides trigonelline, coffee contains other alkaloids that contribute to its stimulant effects and potential health benefits. Coffee is rich in phenolic compounds, such as chlorogenic acids, which have strong antioxidant properties and contribute to reducing inflammation and oxidative stress [30]. Caffeine is the most well-known bioactive component in coffee [31], renowned for its stimulant effects that can improve mental alertness and cognitive performance. It also has been associated with various health benefits, including enhanced physical performance, reduced risk of certain diseases such as Parkinson's and Alzheimer's, and potential protective effects against some cancers [32].

The composition of bioactive components in coffee can vary significantly depending on the coffee bean variety (Arabica and Robusta), coffee subtypes (instant and ground coffee), roasting degree, preparation method (espresso, Americana, latte, mocha, etc.), caffeine content (caffeinated and decaffeinated), and brewing method (boiled, unfiltered, and filtered). Our previous review provides an in-depth discussion of the types of coffee and their specific characteristics [13]. Briefly, Arabica beans generally contain less

caffeine (around 1.5%) compared to Robusta beans (up to 2.7%) [33]. Instant coffee tends to have lower amounts of bioactive compounds compared to ground coffee. The roasting process can alter the levels of certain bioactive compounds, such as increasing the formation of quinides while decreasing chlorogenic acids. Caffeinated and decaffeinated coffees differ in their caffeine content, but decaffeinated coffee still retains many other bioactive compounds. Different brewing methods can significantly affect the concentration of bioactive components. For instance, filtered coffee lacks the rich diterpene compounds found in unfiltered coffee, such as cafestol and kahweol.

Coffee consumption and cancer outcomes in the general population

Skin cancer

There is emerging evidence suggesting a relationship between coffee consumption and a reduced risk of certain types of skin cancer. Wu and colleagues [34] in 2015 evaluated the association between coffee consumption, caffeine intake, and melanoma risk among three large prospective cohort studies (Nurses' Health Study II, NHS II; Nurses' Health Study, NHS; and Health Professionals Follow-up Study, HPFS). The results showed that higher total caffeine intake was associated with a lower risk of melanoma (HR = 0.78, 95% CI, 0.64–0.96) for ≥ 393 mg/day vs. < 60 mg/day; the results were more apparent in women than men and for melanomas at body sites with higher continuous sun exposure than sites with lower continuous sun exposure. These associations were consistent for caffeinated coffee consumption, with no evidence of an association for decaffeinated coffee consumption [34]. In a 2016 evaluation of the Norwegian Women and Cancer (NOWAC) Study, Lukic and colleagues [35] showed that moderate intake of filtered coffee could reduce the risk of malignant melanoma: (HR = 0.80, 95% CI, 0.66–0.98) and (HR = 0.77, 95% CI, 0.61–0.97) for low-moderate (one to three cups/day) and high moderate (> 3–5 cups/day) consumption of filtered coffee, respectively, compared to light consumers of filtered coffee. The was no evidence of effect modification by smoking status, BMI, or average number of sunburns. There were no associations for total, instant, or boiled coffee consumption [35]. Using the Singapore Chinese Health Study, Oh and colleagues [36] in 2019 demonstrated that coffee reduced the risk of nonmelanoma skin cancer (NMSC) in a dose-dependent manner: (HR = 0.47, 95% CI, 0.29–0.75) for all NMSC, (HR = 0.54, 95% CI, 0.31–0.93) for basal cell carcinoma, and (HR = 0.33, 95% CI, 0.13–0.85) for squamous cell carcinoma, comparing ≥ 3 cups/day vs. none to < weekly. The results were modest for caffeine intake [36]. There have been efforts to aggregate findings from individual studies using meta-analyses. In a pooled analysis of nine observational studies, Yew and colleagues [37] in 2016 showed evidence of a beneficial effect of regular coffee consumption on melanoma: (RR = 0.75, 95% CI, 0.63–0.89) for regular coffee drinkers vs. non-regular; there was no significant evidence of an association for decaffeinated coffee drinkers. In another 2016 meta-analysis of 12 observational studies, Wang and colleagues [38] showed that coffee consumption may reduce the risk of cutaneous melanoma: (RR = 0.80, 95% CI, 0.69–0.93), (RR = 0.85, 95% CI, 0.71–1.01), and (RR = 0.92, 95% CI, 0.81–1.05) for the consumption of total coffee, caffeinated coffee, and decaffeinated coffee, respectively, comparing higher with the lowest level of consumption. In a meta-analysis of seven prospective cohort studies, Micek and colleagues [39] in 2018 demonstrated inverse relationships for total coffee and caffeinated coffee consumption with melanoma, with no evidence of an association for decaffeinated coffee: (OR = 0.79, 95% CI, 0.62–1.01), (OR = 0.82, 95% CI, 0.69–0.97), and (OR = 0.94, 95% CI, 0.82–1.08), respectively, comparing the highest vs. lowest category of consumption. In subgroup analyses, the associations were not significantly modified by sex, geographical location, and adjustment for smoking. Total coffee consumption exhibited a linear dose–response relationship with melanoma: (RR = 0.97, 95% CI, 0.95–0.99) per one cup/day increase in total coffee consumption [39].

The evidence suggests an inverse relationship between total coffee consumption and the risk of melanoma and nonmelanoma skin cancer, which may be driven by caffeinated coffee consumption; the lack of an association for decaffeinated coffee consumption is consistent.

Central nervous system cancer

Holick and colleagues [40] in 2010 assessed the associations of coffee and caffeine intake with the risk of adult glioma in three prospective studies (HPFS, NHS I, and NHS II) and showed no significant evidence of associations of total, caffeinated, and decaffeinated coffee consumption with glioma risk. However, caffeine intake was associated with lower risk of glioma in men but not in women: (RR = 0.46, 95% CI, 0.26–0.81) and (RR = 0.91, 95% CI, 0.60–1.40), respectively, comparing the top vs bottom quintiles of intake. Using the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO) prospective study, Hashibe and colleagues [41] in 2015 showed no evidence of an association between caffeine intake and the risk of glioma. Creed and colleagues [42] using the UK Biobank study in 2020 demonstrated modest evidence of associations of total and decaffeinated coffee consumption with the risk of glioma: (HR = 0.71, 95% CI, 0.49–1.05) and (HR = 0.69, 95% CI, 0.47–1.03), respectively, comparing > 4 cups/day vs 0 cup/day.

There appears to be a consistent lack of an association between coffee consumption and risk of central nervous system (CNS) cancers such as gliomas, but this evidence is based on a limited number of studies.

Head and neck cancer

Hashibe and colleagues [41] using the PLCO study showed no evidence of an association between caffeine intake and the risk of head and neck cancer. Gapstur and colleagues [43] in 2017 using the Cancer Prevention Study-II comprising 922,896 participants aged 28–94 years and free of cancer at baseline showed a nonlinear inverse association between coffee consumption and mortality from head and neck cancer among nonsmokers starting at two to three cups/day (HR = 0.72, 95% CI, 0.55–0.95); similar associations were observed at higher levels of consumption.

Collectively, the evidence on the association between coffee consumption and head and neck cancer is limited, but a protective association cannot be ruled out.

Thyroid cancer

Michikawa and colleagues [44] in 2011 analyzed data from a prospective cohort comprising over 100,000 Japanese men and women aged 40–69 years and found no association between coffee consumption and thyroid cancer risk in either sex. Han and Kim [45] in a 2017 meta-analysis of five case–control studies and two cohort studies showed no evidence of an association between coffee consumption and thyroid cancer. However, analysis of hospital-based case–control studies showed a beneficial effect of coffee consumption on thyroid cancer risk: (OR = 0.59, 95% CI, 0.37–0.93) comparing the highest vs. lowest consumption of coffee [45]. In a meta-analysis of six case–control and four cohort studies, Shao and colleagues [46] in 2020 showed an inverse relationship between coffee consumption and thyroid cancer: (RR = 0.75, 95% CI, 0.62–0.91) comparing the highest vs. lowest consumption of coffee. The association was consistent across study design, geographical region, sex, and level of adjustment. In dose–response analysis, the risk of thyroid cancer decreased by 5% per one cup/day increment in coffee consumption (RR = 0.95, 95% CI, 0.91–0.99) [46].

Collectively, the evidence on the association between coffee consumption and thyroid cancer is limited and mostly based on case–control studies.

Lung cancer

Alarmingly, there appears to be a positive association between coffee consumption and lung cancer risk. In 2010, Tang and colleagues [47] pooled the results of five prospective cohort studies and eight case–control studies and reported a positive association between coffee consumption and lung cancer: (RR = 1.27, 95% CI, 1.04–1.54) comparing the highest vs. lowest consumption of coffee consumption; an increase in coffee consumption of two cups/day was associated with a 14% increased risk of developing lung cancer (RR = 1.14, 95% CI = 1.04–1.26). In stratified analyses, the highest coffee consumption was significantly associated with increased risk of lung cancer in prospective studies, but decaffeinated coffee consumption was associated with decreased lung cancer risk (albeit based on a limited number of studies) [47]. Xie and colleagues [48] in 2016 in an updated meta-analysis of five prospective cohort

and 12 case–control studies reported evidence of a positive association between coffee consumption and lung cancer risk: (OR = 1.17, 95% CI, 1.03–1.33) for coffee drinkers compared with nondrinkers; (OR = 1.31, 95% CI, 1.11–1.55) comparing the highest category vs. lowest category of coffee consumption; and (OR = 1.10, 95% CI, 0.92–1.31) for ≤ 1 cup/day, (OR = 1.10, 95% CI, 0.93–1.30) for two to three cups/day, and (OR = 1.20, 95% CI, 1.02–1.39) for ≥ 3 cups/day compared with nondrinkers. The association was not significantly modified by study design, sex, geographical location, smoking status, or year of publication [48]. Ong and colleagues [21] in 2019 evaluated the observational and causal associations of coffee consumption with several cancers as well as overall cancer risk and cancer death using the UK Biobank cohort. Their observational results showed no significant evidence of an association between coffee consumption and lung cancer risk [21]. In a recent meta-analysis which was based on 26 prospective cohort studies, Jin and Je [49] in 2024 still reported a positive association between coffee consumption and lung cancer risk: (RR = 1.30, 95% CI, 1.11–1.53) comparing high vs. low coffee consumption. The association did not vary significantly by sex, geographical location, or smoking status. However, BMI adjustment status significantly modified the association—it was attenuated in a pooled analysis of studies that adjusted for BMI. In another recent pooled analysis of 14 prospective cohort studies, Jabbari and colleagues [19] found evidence of a positive association between coffee consumption and risk of lung cancer: (RR = 1.28, 95% CI, 1.12–1.47) comparing the highest vs. lowest consumption of coffee and (RR = 1.06, 95% CI, 1.03–1.09) for each one cup/day increase in coffee consumption. The positive association was evident in both males and females, though females appeared to have a higher risk than males (p value for interaction = 0.004). Furthermore, there was no significant evidence that adjustment for smoking status modified the association [19].

Breast cancer

In 2009, Tang and colleagues [50] pooled the results of nine cohort and case–control studies and reported modest evidence of an inverse association between coffee consumption and breast cancer risk: (RR = 0.95; 95% CI, 0.90–1.00) comparing the highest vs. lowest consumption of coffee and (RR = 0.98; 95% CI, 0.96–1.00) per increment of two cups/day of coffee consumption. The association did not vary by study design or geographical location [50]. In 2013, Li and colleagues [51] pooled the results of 16 cohort and 10 case–control studies and demonstrated modest evidence of an inverse relationship between coffee consumption and breast cancer: (RR = 0.96, 95% CI, 0.93–1.00) for the highest coffee consumption; (RR = 0.99, 95% CI, 0.95–1.04) for low-to-moderate coffee consumption; and (RR = 0.98, 95% CI, 0.97–1.00) per increment of two cups/day of coffee consumption. The association was not significantly modified by study design, geographical location, and menopausal status. There was a significant inverse relationship between coffee consumption and breast cancer risk in estrogen receptor (ER) negative women, but there was no significant evidence that ER status modified the association [51]. Lukic and colleagues [52] in 2016 employed the Norwegian Women and Cancer (NOWAC) study comprising approximately 92,000 women and found no significant association between coffee consumption and breast cancer risk. In a 2018 meta-analysis of 21 prospective studies, Lafranconi and colleagues [53] showed evidence of a modest inverse association between coffee consumption and breast cancer risk: (RR = 0.96, 95% CI, 0.93–1.00) comparing the highest vs. lowest category of coffee consumption; in the dose–response analysis the estimates were (RR = 0.99, 95% CI, 0.98–1.00) for one cup/day, (RR = 0.98, 95% CI, 0.96–0.99) for two cups/day, (RR = 0.97, 95% CI, 0.94–0.99) for three cups/day, (RR = 0.96, 95% CI, 0.93–0.99) for four cups/day, (RR = 0.95, 95% CI, 0.91–0.98) for five cups/day, (RR = 0.93, 95% CI, 0.89–0.98) for six cups/day, and (RR = 0.92, 95% CI, 0.88–0.98) for seven cups/day. The association between coffee consumption and risk of breast cancer was relatively stronger in postmenopausal women: (RR = 0.90, 95% CI, 0.82–0.99) for four cups/day. The association was not significantly modified by coffee type, geographical location, ER status, menopausal status, BMI, duration of follow-up, and adjustment status for smoking, alcohol, physical activity, or education [53]. Ong and colleagues [21] in 2019 in their evaluation of the UK Biobank cohort found no significant evidence of an association between coffee consumption and breast cancer risk. Li and Ma [54] in 2021 pooled results

of 17 cohort and nine case–control studies published between 2005 and 2020 and showed evidence of a modest inverse relationship between coffee consumption and breast cancer risk: cancer risk (RR = 0.95, 95% CI, 0.92–0.99) comparing the highest vs. lowest consumption of coffee. The association was not significantly modified by coffee type, study design, geographical location, ER status, menopausal status, BMI, and adjustment status for smoking, alcohol, BMI, oral contraceptive use or history of benign breast disease [54]. Using the Women's Health Initiative cohort comprising 77,688 postmenopausal women, Yaghjyan and colleagues [55] in 2022 found no associations of coffee consumption with breast cancer risk and for ER/progesterone receptor (PR)-defined tumor subtypes. However, higher caffeine consumption was modestly and positively associated with the overall breast cancer risk and with ER + / PR + tumors [55].

The association between coffee consumption and breast cancer is not conclusive, but a weak to modest inverse association cannot be ruled out.

Gastrointestinal cancer

In a 2023 prospective evaluation of the VETS cohort, Vainshelboim and Myers [56] showed that higher CRF was associated with a lower risk of digestive system cancer incidence in the entire cohort of men (HR = 0.94, 95% CI, 0.91–0.98 per 1-MET increase), particularly in those < 60 years (HR = 0.91, 95% CI, 0.85–0.97 per 1-MET increase), never smokers (HR = 0.91, 95% CI, 0.83–1.00 per 1-MET increase), and current smokers (HR = 0.91, 95% CI, 0.84–0.99 per 1-MET increase). There was no association in men ≥ 60 years old and among former smokers.

Mouth, pharyngeal, laryngeal, and esophageal cancers

The evidence on the relationship between coffee consumption and mouth, pharyngeal, laryngeal, and esophageal cancers is mixed and mostly based on case–control studies. In a cohort of approximately 40,000 participants from the Miyagi Cohort Study in Japan, Naganuma and colleagues [57] in 2008 demonstrated that coffee consumption was associated with a lower risk of oral, pharyngeal, and esophageal cancers: (HR = 0.51, 95% CI, 0.33–0.77) comparing ≥ 1 cup/day vs. no consumption. The association was consistent irrespective of sex, cancer site, and smoking status. In the Cancer Prevention Study-II, a two cup/day increase in coffee consumption was associated with an increased risk of esophageal cancer-related death among nonsmokers (HR = 1.07, 95% CI, 1.02–1.12) [43]. In 2011, Turati and colleagues [58] pooled the results of one cohort and eight case–control studies to evaluate the associations of coffee consumption with cancers of the oral cavity/pharynx and larynx, esophageal squamous cell carcinoma, and esophageal adenocarcinoma. The authors reported an inverse association between coffee consumption and cancer of the oral cavity/pharynx (RR = 0.64, 95% CI, 0.51–0.80) for the highest vs. lowest category of coffee consumption) with no evidence of associations for laryngeal cancer, esophageal squamous cell carcinoma, and esophageal adenocarcinoma. In a pooled analysis of one cohort and seven case–control studies, Ouyang and colleagues [59] in 2014 showed no evidence of an association between coffee consumption and risk of laryngeal cancer. Chen and Long [60] in 2014 also pooled the results of one cohort and five case–control studies and showed that coffee consumption was associated with an increased risk of laryngeal cancer: (RR = 1.47, 95% CI, 1.03–2.11) comparing the highest vs. lowest coffee consumption and (RR = 1.22, 95% CI, 1.04–1.54) per one cup/day increment in coffee consumption. Among 442,143 men and women without cancer at baseline from nine countries of the European Prospective Investigation into Cancer and Nutrition (EPIC), Zamora-Ros and colleagues [61] in 2014 showed no evidence of significant associations between coffee consumption and the risk of esophageal cancer, adenocarcinoma, and squamous cell carcinoma. In stratified analysis, coffee consumption was inversely associated with esophageal squamous cell carcinoma in men and current smokers [61]. In a pooled analysis of four cohort and 11 case–control studies, Li and colleagues [62] in 2016 demonstrated an inverse association between coffee consumption and oral cancer: (OR = 0.63, 95% CI, 0.52–0.75) overall; (OR = 0.60, 95% CI, 0.49–0.74) for case–control studies; and (OR = 0.66, 95% CI, 0.45–0.98) for cohort studies, comparing the highest vs. lowest categories of coffee consumption. In 2017, Miranda and colleagues [63] pooled results of four cohort and 13 case–control studies and showed inverse associations between high coffee consumption and the risk of oral and pharyngeal cancers: (OR = 0.69,

95% CI, 0.57–0.84) for oral and pharyngeal cancer grouped together; (OR = 0.82, 95% CI, 0.58–1.16) for oral cavity cancer; and (OR = 0.72, 95% CI, 0.54–0.95) for pharyngeal cancer, comparing high vs. low coffee consumption. In a meta-analysis of two cohort and nine case–control studies, Zhang and colleagues [64] in 2018 demonstrated no evidence of an association between heavy coffee consumption and esophageal cancer. However, stratified analyses showed an inverse association in East Asian participants with no evidence of an association in Euro-American participants [64].

Gastric cancer

In 2006, Botelho and colleagues [65] pooled the results of 23 cohort and case–control studies and found no evidence of a significant association between coffee consumption and gastric cancer risk. Li and colleagues [66] in 2015 pooled results of 13 prospective cohort studies and observed no significant evidence of an association between coffee consumption and gastric cancer risk. The association was not significantly modified by sex, study quality, geographical location, follow-up duration, and adjustment status for several confounders [66]. Zeng and colleagues [67] in 2015 pooled results of nine cohort and found no significant evidence of an association between coffee consumption and gastric cancer risk. The association was not significantly modified by sex, study quality, geographical location, and adjustment status for smoking or alcohol [67]. Liu and colleagues [68] in 2015 pooled the results of nine cohort studies and found no significant evidence of an association between coffee consumption and gastric cancer risk. However, subgroup analysis by anatomic location showed a positive association between coffee consumption and gastric cardia cancer, though there was no significant evidence of an interaction effect [68]. In 2016, Xie and colleagues [69] pooled the results of nine cohort and 13 case–control studies and showed no overall evidence of an association between coffee consumption and gastric cancer risk. Stratified analysis suggested inverse associations in case–control studies and studies published over the last 10 years, but there was no suggestion of an interaction effect [69]. Deng and colleagues [70] in 2016 pooled the results of 13 cohort studies and found evidence of a positive association between coffee consumption and gastric cancer risk: (RR = 1.16, 95% CI, 1.03–1.32) comparing the highest vs. lowest consumption of coffee. However, the association seemed to be driven by gastric cardiac cancer and was attenuated when smoking was accounted for [70]. In a pooled analysis of 18 prospective cohort studies, Song and colleagues [71] in 2022 showed no significant evidence of an association between coffee consumption and gastric cancer risk. The association was not significantly modified by sex, geographical location, and adjustment status for smoking, alcohol, BMI, tea, age, or physical activity [71]. Using data from an international consortium of observational studies on gastric cancer (18 studies), Martimianaki and colleagues [72] in 2022 found no evidence for an association between coffee consumption and overall gastric cancer risk. However, there was evidence of a positive association between coffee consumption and gastric cardia cancer: (OR = 1.61, 95% CI, 1.27–2.05) comparing ≥ 5 cups/day vs. never or rare coffee consumption [72].

Taken together, there is no significant association between coffee consumption and gastric cancer risk; however, an association between higher coffee consumption and increased gastric cardia cancer risk cannot be ruled out.

Pancreatic cancer

The overall evidence suggests there is no association between coffee consumption and pancreatic cancer, but a positive association cannot be ruled out. In a pooled analysis of 17 cohort and 37 case–control studies, Turati and colleagues [73] in 2012 demonstrated no significant evidence of an association between coffee consumption and pancreatic cancer. This association did not vary by study design, sex, geographical location, and smoking status [73]. Bhoo-Pathy and colleagues [74] utilized the EPIC cohort, comprising 477,312 participants without cancer and showed that total coffee and decaffeinated coffee consumption were not associated with pancreatic cancer risk. Li and colleagues [18] in a 2019 meta-analysis of 12 cohort studies showed evidence of an association between increased coffee consumption and increased risk of pancreatic cancer: (RR = 1.06, 95% CI, 1.05–1.07) per increment of one cup/day of coffee consumption. Zhou and colleagues [75] in 2019 assessed the

association between coffee consumption and risk of pancreatic cancer among never-smokers using the UK prospective Million Women Study and found no evidence of an association; a meta-analysis of results from this cohort and three smaller prospective studies still did not show evidence of an association. In a pooled analysis of 12 cohort studies, Bae and colleagues [76] in 2020 found no evidence of an association between coffee consumption and pancreatic cancer risk. The association was not significantly modified by year of publication, sex, and adjustment status for BMI or history of diabetes [76].

Liver cancer

Kennedy and colleagues [77] in 2017 pooled the results of 18 cohort and eight case–control studies and showed that coffee consumption was associated with a reduction in risk of hepatocellular carcinoma (HCC): (RR = 0.65, 95% CI, 0.59–0.72) per two cups/day increment in coffee consumption. The respective estimates were (RR = 0.71, 95% CI, 0.65–0.77) for cohort studies; (RR = 0.53, 95% CI, 0.41–0.69) for case–control studies; (RR = 0.73, 95% CI, 0.63–0.85) for caffeinated coffee; and (RR = 0.86, 95% CI, 0.74–1.00) for decaffeinated coffee. The association did not vary by liver disease or the presence/absence of high alcohol consumption, high BMI, type 2 diabetes mellitus, smoking, or hepatitis B and C viruses [77]. Godos and colleagues [78] in 2017 in a pooled analysis of 13 cohort and case–control studies showed increased coffee consumption to be associated with decreased risk of liver cancer: (RR = 0.85, 95% CI, 0.82–0.88) per one cup/day increment in coffee consumption. Bhurwal and colleagues [79] in 2020 pooled 20 cohort and case–control studies and showed that coffee consumption reduced the risk of HCC or liver cancer: (RR = 0.69, 95% CI, 0.56–0. 85) for any amount of coffee consumption; (RR = 0.76, 95% CI, 0.55–1.04) for up to one cup/day; (RR = 0.64, 95% CI, 0.43–0.96) for up to two cups/day; and (RR = 0.51, 95% CI, 0.38–0.69) for up to three cups/day, compared with nondrinkers.

There is a protective association between coffee consumption and liver cancer, which is consistent with a dose–response relationship.

Bile ducts and gall bladder cancer

The evidence is mixed for gall bladder cancer, with consistent evidence showing no association for biliary tract cancer. Makiuchi and colleagues [80] in 2016 utilized a prospective cohort comprising approximately 99,000 participants and demonstrated no association between coffee consumption and the risk of biliary tract, gallbladder, or extrahepatic bile duct cancer. In a prospective cohort study of 72,680 Swedish adults, Larsson and colleagues [81] in 2017 showed that coffee consumption was associated with a reduced risk of gallbladder cancer: (HR = 0.76, 95% CI, 0.41–1.41) for two cups/day; (HR = 0.50, 95% CI, 0.24–1.06) for three cups/day; and (HR = 0.41, 95% CI, 0.20–0.83) for ≥ 4 cups/day, compared with one or less cup/day. Godos and colleagues [78] in 2017 in a pooled analysis of five studies found no evidence of an association between coffee consumption and biliary tract cancer. Huang and colleagues [82] in 2024 pooled data from 15 studies in the Biliary Tract Cancers Pooling Project and showed that coffee consumption was positively associated with gall bladder cancer: (HR = 1.29, 95% CI, 1.01–1.66) for < 3 cups/day and (HR = 1.49, 95% CI, 1.11–1.99) for ≥ 3 cups/day compared to nondrinkers. There was little evidence of associations between coffee consumption and other biliary tract cancers [82].

Colorectal cancer

Most of the evidence on the association between coffee consumption and risk of colorectal cancer (CRC) have been based on case–control studies [83]. Giovannucci [84] in 1998 pooled the results of five cohort studies and 12 case–control studies and showed inconsistencies in the associations: (RR = 0.97, 95% CI, 0.73–1.29) for cohort studies, (RR = 0.72, 95% CI, 0.61–0.84) for case–control studies, and (RR = 0.76, 95% CI, 0.66–0.89) for the combined results, comparing the highest vs. lowest intake of coffee. The author noted that the combined result was largely driven by case–control studies, which are characterized by several biases. A number of studies have also pooled results from cohort and case–control studies and showed inverse associations for case–control studies, but not cohort studies [85–87]. Kashino and colleagues [88] in 2018 pooled the results of eight cohort studies conducted in Japan

and showed that coffee consumption was not significantly associated with CRC risk in men or women. Ong and colleagues [21] in 2019 in their evaluation of the UK Biobank cohort found modest evidence of an inverse association between coffee consumption and CRC: (OR = 0.97, 95% CI, 0.94–0.99) per one cup/day increase in coffee consumption. In 2019, Sartini and colleagues [89] pooled the results of 26 cohort studies and showed no significant evidence of an association between coffee consumption and CRC. Their stratified analysis suggested a protective effect for colon but not rectal cancer and a protective effect of decaffeinated coffee on CRC; however, these subgroup results were based on a pooled analysis of two to three studies [89]. In 2020, Um and colleagues [90] used the Cancer Prevention Study-II Nutrition Cohort and showed that higher consumption of decaffeinated coffee was associated with lower risk of CRC, whereas caffeinated coffee was modestly associated with higher risk of rectal cancer: decaffeinated coffee—(HR = 0.82, 95% CI, 0.69–0.96) for overall colorectal cancer, (HR = 0.82, 95% CI, 0.69–0.99) for colon cancer, and (HR = 0.63, 95% CI, 0.40–0.99) for rectal cancer, comparing ≥ 2 cups/day vs nondrinkers; caffeinated coffee—(HR = 1.37, 95% CI, 0.99–1.89) for rectal cancer, comparing ≥ 2 cups/day vs nondrinkers. Wang and colleagues [91] in 2020 pooled the results of two cohort and six case–control studies and showed an inverse association between coffee consumption and colorectal adenoma: (OR = 0.70, 95% CI, 0.55–0.90) comparing the highest vs. lowest coffee intake. Using the Korean Health Examinees Study comprising 114,243 participants, Na and colleagues [20] in 2022 found no significant evidence of an association between coffee and the risk of CRC.

Collectively, the evidence on a potential protective association between coffee consumption and CRC is mostly based on case–control study designs; evidence from cohort studies is inconclusive or suggests no association.

Genitourinary cancer

Prostate cancer

Park and colleagues [92] in 2010 pooled the results of four cohort and eight case–control studies and showed evidence of an increased risk of prostate cancer with higher coffee consumption, which appeared to be driven by case–control designs: (RR = 1.16, 95% CI, 1.01–1.33) for combined study designs, (RR = 1.21, 95% CI, 1.03–1.43) for case–control studies, and (RR = 1.06, 95% CI, 0.83–1.35) for cohort studies, comparing the highest vs. lowest coffee consumption. In a 2014 meta-analysis of nine cohort and 12 case–control studies, Lu and colleagues [93] reported evidence of an inverse association between coffee consumption and prostate cancer risk: (OR = 0.91, 95% CI, 0.86–0.97) for all studies combined, (OR = 0.89, 95% CI, 0.84–0.95) for cohort studies, and (OR = 1.10, 95% CI, 0.95–1.26) for case–control studies, comparing the highest vs. lowest consumption of coffee. In pooled results of 13 cohort studies, Huang and colleagues [94] in 2014 reported an inverse association between coffee consumption and prostate cancer risk: (RR = 0.86, 95% CI, 0.79–0.95) comparing the highest vs. lowest consumption of coffee. Cao and colleagues in a pooled analysis of ten cohort studies showed a decreased risk of prostate cancer with coffee consumption: (RR = 0.88, 95% CI, 0.82–0.95) comparing regular coffee drinkers with seldom or never drinkers. Liu and colleagues [95] in 2015 pooled the results of 13 cohort studies and showed evidence of an inverse association between coffee consumption and prostate cancer risk: (RR = 0.90, 95% CI, 0.85–0.95) comparing the highest vs. lowest coffee intake and (RR = 0.98, 95% CI, 0.96–1.00) for every two cups/day increment in coffee consumption. The association did not vary significantly by geographical location, publication year, degree of adjustment, and grade of cancer. Xia and colleagues [96] in their 2017 pooled analysis of 14 cohort and case–control studies observed no evidence of an effect of coffee consumption on prostate cancer risk overall and when grouped according to study design. Ong and colleagues [21] in 2019 in their evaluation of the UK Biobank cohort found modest evidence of an inverse association between coffee consumption and prostate cancer: (OR = 0.98, 95% CI, 0.96–1.00) per one cup/day increase in coffee consumption. Chen and colleagues [97] in 2021 pooled the results of 16 prospective cohort studies and showed that higher coffee consumption was associated with a lower risk of prostate cancer: (RR = 0.91, 95% CI, 0.84–0.98) comparing the highest vs. lowest category of coffee consumption and (RR = 0.988, 95% CI, 0.981–0.995) for each increment of one cup/day of coffee.

Collectively, increased coffee consumption decreases the risk of prostate cancer, and the evidence appears consistent.

Kidney cancer

There is mostly consistent evidence showing no association between coffee consumption and kidney cancer. Huang and colleagues [94] in 2014 pooled the results of four cohort studies and reported no evidence of an association between coffee consumption and kidney cancer risk. Wijarnpreecha and colleagues [98] in 2017 pooled the results of six cohort and 16 case–control studies and reported no significant association between coffee consumption and renal cell carcinoma. Ong and colleagues [21] in 2019 in their evaluation of the UK Biobank cohort found no significant evidence of an association between coffee consumption and kidney cancer. Rhee and colleagues [99] in 2021 utilized the National Institutes of Health-American Association of Retired Persons Diet and Health Study comprising 420,118 participants and reported evidence of a protective effect of coffee consumption on renal cell cancer risk: HRs of 0.94 (95% CI, 0.81–1.09), 0.94 (95% CI, 0.81–1.09), 0.80 (95% CI, 0.70–0.92), and 0.77 (95% CI, 0.66–0.90) for usual coffee intake of <1, one, two to three, and ≥ 4 cups/day, respectively. The association was modified by smoking status—there was an inverse relationship among never-smokers, with no relationship observed in non-smokers [99]. Chen and colleagues [100] in 2022 used the Japan Public Health Center-based Prospective Study comprising 102,463 participants and reported no evidence of an association between coffee consumption and kidney cancer. In 2022, Rhee and colleagues [101] in a meta-analysis of 10 cohort studies reported an inverse association between coffee consumption and renal cancer: (RR = 0.88, 95% CI, 0.78–0.99) comparing the highest vs. lowest category of coffee consumption. However, of the 10 pooled studies, only two reported significant inverse associations [99, 102], and the pooled results were mainly driven by one of these studies which reported a RR of 0.30 (95% CI, 0.11–0.79) [102]. Furthermore, the results were not robust to influence (i.e., sensitivity) analyses [101].

Bladder cancer

The relationship between coffee consumption and bladder cancer has been studies extensively, with mixed results. Yu and colleagues [103] in 2011 pooled the results of 40 independent cohort studies to assess the associations between coffee consumption and overall and site-specific cancers. Their subgroup analysis involving nine studies showed an inverse association between coffee consumption and bladder cancer: (RR = 0.83, 95% CI, 0.73–0.94) comparing the highest vs. lowest intake of coffee. In 2012, Zhou and colleagues [104] conducted a dose–response meta-analysis of five cohort and 23 case–control studies and showed evidence of a positive association between coffee consumption and bladder cancer risk in case–control studies, but none for cohort studies: Cohort studies: (RR = 1.09, 95% CI, 0.89–1.34) for one cup/day, (RR = 1.13, 95% CI, 0.82–1.55) for two cups/day, (RR = 1.09, 95% CI, 0.77–1.56) for three cups/day, and (RR = 1.01, 95% CI, 0.69–1.48) for four cups/day, compared with non-drinkers; case–control studies: (RR = 1.07, 95% CI, 1.02–1.13) for one cup/day, (RR = 1.15, 95% CI, 1.05–1.26) for two cups/day, (RR = 1.22, 95% CI, 1.08–1.38) for three cups/day, and (RR = 1.29, 95% CI, 1.12–1.48) for four cups/day [104]. Huang and colleagues [94] in 2014 pooled the results of five cohort studies and reported no evidence of an association between coffee consumption and kidney cancer risk. Wu and colleagues [105] in 2015 pooled the results of six cohort studies and 34 case–control studies and showed evidence of an increased risk between coffee consumption and bladder cancer, which was driven by male coffee drinkers and non-smoking coffee drinkers: (OR = 1.05, 95% CI, 1.03–1.06) for case–control studies and (OR = 1.03, 95% CI, 0.99–1.06) for cohort studies per increase in one cup/day; (OR = 1.31, 95% CI, 1.08–1.59) for male coffee drinkers, (OR = 1.30, 95% CI, 0.87–1.96) for female coffee drinkers; (OR = 1.24, 95% CI, 0.91–1.70) for smoking coffee drinkers; and (OR = 1.72, 95% CI, 1.25–2.35) for non-smoking coffee drinkers [105]. In a pooled analysis of the Miyagi Cohort Study and the Ohsaki Cohort Study comprising 73,346 individuals, Sugiyama and colleagues [106] in 2017 reported a significant inverse association between coffee consumption and the risk of bladder cancer: (HR = 1.22, 95% CI, 0.90–1.66) for occasional coffee drinkers,

(HR = 0.88, 95% CI, 0.61–1.26) for one to two cups/day, and (HR = 0.56, 95% CI, 0.32–0.99) for ≥ 3 cups/day, compared with non-drinkers. Dai and colleagues [107] in 2019 pooled the results of 16 prospective cohort studies and showed no evidence of an association, which was consistent across sex and smoking status subgroups; there was evidence of a positive association among studies that did not adjust for smoking. In 2020, Yu and colleagues [108] conducted an individual participant data meta-analysis of 12 cohort studies and reported evidence of positive associations between coffee consumption and bladder cancer among male smokers but not never smokers and females: (HR = 1.75, 95% CI, 1.27–2.42) for male current smokers and (HR = 1.44, 95% CI, 1.12–1.85) for male former smokers, comparing > 500 ml/day (equivalent to > 4 cups/day) coffee consumption with non-drinkers.

In summary, while there is some evidence to suggest an association between increased coffee consumption and increased risk of bladder cancer, particularly in men, the relationship is not definitive, and further research is needed to clarify these findings.

Endometrial cancer

Numerous observational studies and meta-analyses have been conducted on the relationship between coffee consumption and endometrial cancer. Je and colleagues [109] in 2011 prospectively assessed coffee consumption in relation to endometrial cancer risk using the NHS and showed an inverse association: (RR = 0.75, 95% CI, 0.57–0.97) comparing ≥ 4 cups/day vs < 1 cup/day. The association was similar for caffeinated coffee consumption. In a pooled analysis of six cohort and 10 case–control studies, Je and Giovannucci [110] in 2012 showed increased coffee intake consumption to be associated with a reduced risk of endometrial cancer, which was consistent for cohort and case–control studies: (RR = 0.71, 95% CI, 0.62–0.81) for overall, (RR = 0.70, 95% CI, 0.61–0.80) for cohort studies, and (RR = 0.69, 95% CI, 0.55–0.87) for case–control studies, for the highest vs. lowest categories of coffee intake. In 2015, Zhou and colleagues [111] pooled the results of 13 prospective cohort studies and showed that coffee and caffeine intake were associated with reduced risk of endometrial cancer, consistent with linear dose–response relationships, and the associations might be modified by BMI and history of hormone therapy: (RR = 0.80, 95% CI, 0.74–0.86) for total coffee, (RR = 0.66, 95% CI, 0.52–0.85) for caffeinated coffee, and (RR = 0.77, 95% CI, 0.63–0.94) for decaffeinated coffee, comparing the highest vs. lowest intake. Stronger associations were found among those who were never treated with hormones and those with a BMI ≥ 25 kg/m^2 [111]. Ong and colleagues [21] in 2019 in their evaluation of the UK Biobank cohort found no significant evidence of an association between coffee consumption and endometrial cancer. In an IPD meta-analysis of six cohort and 13 case–control studies, Crous-Bou and colleagues [17] in 2022 reported a linear dose–response relationship between higher coffee consumption and lower risk of endometrial cancer: (OR = 0.90, 95% CI, 0.82–1.00) for one cup/day, (OR = 0.86, 95% CI, 0.78–0.95) for two to three cups/day, and (OR = 0.76, 95% CI, 0.66–0.87) for > 4 cups/day, compared with non-drinkers. The inverse association between coffee consumption and endometrial cancer did not vary by smoking or diabetes status, but BMI significantly modified the association; the inverse association was stronger in participants with BMI > 25 kg/m [2, 17].

Overall, the evidence shows that moderate to high coffee consumption is associated with a reduced risk of endometrial cancer.

Ovarian cancer

In 2007, Silvera and colleagues [112] examined ovarian cancer risk in association with coffee consumption in a prospective cohort study of approximately 50,000 Canadian women enrolled in the National Breast Screening Study and found no strong evidence of an association. Braem and colleagues [113] in 2012 conducted a prospective analysis of the EPIC cohort study as well as an updated meta-analysis of five published prospective cohort studies and found no evidence to support an association between coffee consumption and risk of ovarian cancer. Lukic and colleagues [52] in 2016 employed the NOWAC study and found no significant association between coffee consumption and ovarian cancer risk. In a dose–response meta-analysis of eight prospective cohort studies, Berretta and colleagues [114] in 2018 found no evidence of an association between coffee consumption and the risk of ovarian cancer. Ong and colleagues [21] in 2019 in their evaluation of the UK

Biobank cohort found no significant evidence of an association between coffee consumption and ovarian cancer. In a pooled analysis of 14 prospective cohort studies, Salari-Moghaddam and colleagues [115] in 2019 found no evidence of a statistically significant association between caffeine intake or different types of coffee and the risk of ovarian cancer. Using data from the PLCO cohort, Huang and colleagues [116] in 2024 showed that a higher consumption of coffee or caffeine was associated with a reduced risk of ovarian cancer: coffee consumption—(HR = 0.66, 95% CI, 0.44–0.99) for two to three cups/day and (HR = 0.59, 95% CI, 0.36–0.97) for ≥ 4 cups/day compared with no consumption; caffeine consumption—(HR = 0.61, 95% CI, 0.41–0.90) for 458.787 mg/day compared with no consumption. The associations did not vary across several subgroups including age, sex, BMI, smoking, contraceptive use, hormone therapy, family history of ovarian cancer, diabetes, hypertension, and physical activity [116].

Taken together, the relationship between coffee consumption and ovarian cancer remains inconclusive. While some research suggests a potential protective effect, most studies have found no significant association.

Hematological malignancies

Leukemia

The relationship between coffee consumption and leukemia has not been as extensively studied. Ugai and colleagues [117] investigated the association of coffee consumption and the risk of acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS) using the Japan Public Health Center-based (JPHC) Prospective Study which comprised approximately 96,000 participants. The results showed no significant association between coffee consumption and the risk of AML. However, a decreasing dose–response relationship was observed between coffee consumption and the risk of MDS among men, with a HR of 0.83 (95% CI, 0.43–1.62) for one to four times per week and 0.47 (95% CI, 0.22–0.99) for daily consumption compared to almost none [117]. Taken together, the evidence on the relationship between coffee consumption and leukemia is limited, and more research is needed to draw definitive conclusions.

Myeloma

Multiple myeloma is a type of blood cancer that primarily affects older adults, making it a significant disease of aging [118]. It originates in transformed plasma cells, which accumulate in the bone marrow, disrupting normal blood cell production and leading to a range of serious health issues, including anemia, bone pain, fractures, kidney dysfunction, and increased susceptibility to infections [118, 119]. The incidence of multiple myeloma increases sharply with age, with the median age at diagnosis being around 70 years [118]. Age-related changes in the immune system, such as immunosenescence and chronic inflammation, contribute to the higher risk and poorer prognosis in older individuals [118]. Research on the association between coffee consumption and multiple myeloma is limited. Ugai and colleagues employed the JPHC study to explore this relationship but found no significant association between coffee consumption and the risk of multiple myeloma [120]. Given the scarcity of studies in this area, the evidence remains inconclusive, underscoring the need for further research to better understand any potential links between coffee intake and the risk of developing myeloma.

Hodgkin's and Non-Hodgkin's lymphoma

Han and colleagues [121] in a 2016 meta-analysis of three cohort and four case–control studies showed no evidence to support an association between coffee consumption and the risk of lymphoma. Ugai and colleagues [120] in 2017 employed the JPHC study and observed no significant association between coffee consumption and the risk of malignant lymphoma. Ong and colleagues [21] in 2019 in their evaluation of the UK Biobank cohort found no significant evidence of an association between coffee consumption and lymphoma. In a meta-analysis of six cohort and nine case–control studies, Mirtavoos-Mahyari and colleagues [122] in 2019 showed no evidence of an association between coffee consumption and the risk of non-Hodgkin lymphoma (NHL). In analyses of approximately 75,000 postmenopausal women from the Women's Health Initiative Observational Study, Wang and colleagues [123] in 2022 showed no evidence of an association between coffee consumption and NHL risk, irrespective of the total amount of

daily coffee intake, coffee types, or coffee preparation methods.

Findings albeit based on a limited number of studies suggest no evidence of an association between coffee consumption and risk of lymphoma.

Overall cancer incidence and mortality

The relationship between coffee consumption and overall cancer incidence and cancer mortality is mixed. In a pooled analysis of 10 prospective cohorts, Malerba and colleagues [124] in 2013 showed no evidence of an association between coffee consumption and cancer mortality. In a dose–response meta-analysis of 21 prospective cohort studies, Crippa and colleagues [125] in 2014 demonstrated no evidence of an association between coffee consumption and cancer mortality. In 2015, Hashibe and colleagues [41] utilized the PLCO cohort and showed that coffee intake was not associated with the risk of all cancers combined. Utilizing the NOWAC cohort, Lukic and colleagues [52] showed evidence that coffee consumption might modestly increase the risk of overall cancer incidence: (HR = 1.11, 95% CI, 0.99–1.23) comparing > 7 cups/day versus ≤ 1 cup/day.

In a 2016 dose–response meta-analysis of 15 cohort studies, Grosso and colleagues [126] observed no association between coffee consumption and cancer mortality overall. However, stratification by smoking status showed that cancer mortality was significantly decreased only when considering non-smokers, while increased in smokers: (RR = 0.79, 95% CI, 0.74–0.85) for non-smokers and (RR = 1.14, 95% CI, 1.04–1.24) for smokers, comparing seven cups/day with non-drinkers [126]. Loftfield and colleagues [14] utilized the UK Biobank and showed that coffee consumption was inversely associated with cancer mortality: (HR = 0.87, 95% CI, 0.79–0.96) comparing six to seven cups/day vs non-drinkers. The association was similar for instant, ground, and decaffeinated coffee, and was not modified by genetic variation in caffeine metabolism [14]. Ong and colleagues [21] in 2019 evaluated the observational and causal associations of coffee consumption with overall cancer risk and cancer death using the UK Biobank cohort. Their observational results showed that coffee consumption was not associated with overall risk of being diagnosed with or dying from cancer: (OR = 0.99, 95% CI, 0.98–1.00) for overall cancer and (OR = 1.01, 95% CI, 0.99–1.03) for cancer death, per one cup/day [21]. These associations were similar in males and females and did not vary by smoking status [21]. In 2022, Shin and colleagues [127] pooled data based on 12 prospective cohorts from the Asia Cohort Consortium conducted in China, Japan, Korea, and Singapore and showed an inverse association between coffee consumption and death from cancer: men—(HR = 0.88, 95% CI, 0.84–0.93) for < 1 cup/day, (HR = 0.86, 95% CI, 0.81–0.92) for one to < 3 cups/day, (HR = 0.88, 95% CI, 0.79–0.97) for three to < 5 cups/day, and (HR = 0.85, 95% CI, 0.75–0.97) for ≥ 5 cups/day, compared with almost never; Women—(HR = 0.91, 95% CI, 0.86–0.97) for < 1 cup/day, (HR = 0.90, 95% CI, 0.81–1.00) for one to < 3 cups/day, (HR = 0.75, 95% CI, 0.57–0.98) for three to < 5 cups/day, and (HR = 0.81, 95% CI, 0.63–1.04) for ≥ 5 cups/day, compared with almost never. The inverse associations were similar across age, smoking status, alcohol use, BMI, education level, and history of comorbidities [127].

Cancer recurrence in individuals with a prior diagnosis of cancer

In 1997, Baron and colleagues [128] showed no evidence of an association between the intake of regular coffee or decaffeinated coffee with the risk of recurrent colorectal adenomas. Geybels and colleagues [129] in 2013 investigated associations of pre-diagnostic coffee with the risk of prostate cancer recurrence/progression in 630 patients who had been diagnosed with prostate cancer and showed a reduced risk of prostate cancer recurrence/progression with coffee consumption: (HR = 0.41, 95% CI, 0.20–0.81) comparing ≥ 4 cups/day with ≤ 1 cup/week. Guercio and colleagues [130] in 2015 examined the effect of coffee consumption on cancer recurrence in 953 patients with stage III colon cancer and showed that higher coffee intake was associated with reduced risk of cancer recurrence: (HR = 0.58, 95% CI, 0.34–0.999) for total coffee and (HR = 0.48, 95% CI, 0.25–0.91) for caffeinated coffee, comparing ≥ 4 cups/day with abstainers. There was no evidence of an association for decaffeinated coffee [130]. Oyelere and colleagues [131] in 2024 used data from a prospective cohort study of 1719 stage I–III

CRC patients in the Netherlands and showed that coffee consumption may be associated with a lower risk of CRC recurrence: (HR = 0.68, 95% CI, 0.49–0.94) comparing ≥ 4 cups/day with < 2 cups/day.

In summary, current evidence suggests that coffee consumption might reduce the risk of cancer recurrence, particularly in colorectal cancer.

Evidence from Mendelian randomization studies

Mendelian randomization studies have played a significant role in exploring the relationship between coffee consumption and cancer risk. These studies use genetic variants (single nucleotide polymorphisms (SNPs)) as instrumental variables to infer causality, helping to overcome confounding factors and reverse causation that are common in observational studies [132]. The progress in genome-wide association studies (GWAS) has paved the way for MR studies focusing on coffee and health, by uncovering several genetic variants linked to self-reported regular coffee and caffeine intake [133]. There are several MR studies that have assessed the causal relevance of coffee or caffeine consumption to overall and site-specific cancers (Table 1).

In 2017, Taylor and colleagues [134] published the first MR study on coffee consumption and cancer risk. Using two genetic variants robustly associated with caffeine intake as proxies for coffee consumption in a sample of men of European ancestry from 25 studies, the authors showed no clear evidence of a causal association between coffee consumption and prostate cancer risk and progression. Furthermore, there was no clear evidence that the association varied between ever and never smokers [134]. Using genetic data on individuals of European ancestry from the Ovarian Cancer Association Consortium and combined instrumental variable estimates, Ong and colleagues [135] in 2018 found no evidence indicative of a strong association between epithelial ovarian cancer risk and genetically predicted coffee or caffeine levels. In the 2019 study by Ong and colleagues [21], meta-analysis of their MR findings (using UK Biobank data) with publicly available summary data on various cancers did not support strong causal relationships between coffee consumption and risk of overall cancer incidence and mortality and several site-specific cancers, though weak associations could not be ruled out for ovarian (protective effect), prostate (protective effect), and lung cancer (increased risk). The associations did not vary by sex or smoking status [21]. Using 33 variants for coffee consumption from a GWAS of UK Biobank participants and publicly available GWAS summary statistics from the Breast Cancer Association Consortium, Ellingjord-Dale and colleagues [136] in 2021 reported findings that did not support an association of genetically predicted coffee consumption with breast cancer risk, but which could not rule out the existence of a weak association. Wang and colleagues [137] in 2021 reported no evidence of a causal relationship between coffee consumption and prostate cancer risk in their MR analyses which employed primary and secondary genetic instruments. In an MR study to explore the potential causal associations between dietary habits and HCC risk in an East Asian population, Deng and colleagues [138] in 2022 reported genetically predicted coffee consumption to be inversely related to HCC risk. Carter and colleagues [22] in 2022 investigated the associations between genetically predicted coffee consumption and any cancer and 22 site-specific cancers using data from individuals of European-descent in UK Biobank. Twelve independent SNPs were used as proxies for coffee consumption. The results showed that there was no strong evidence supporting a causal relationship between genetically predicted coffee consumption and the majority of cancers studied, except for an increased risk of esophageal cancers and multiple myeloma, and a decreased risk of ovarian cancers, findings which remained consistent after adjustment for genetically predicted BMI, smoking, and alcohol consumption [22]. Using 12 SNPs strongly associated with coffee consumption and summary-level data on genetic variation in bladder cancer obtained from the UK Biobank and FinnGen consortium, Deng and colleagues [139] in 2022 showed no evidence of a causal association between habitual coffee consumption and bladder cancer risk. Using publicly available summary-level GWAS data and data from BioBank Japan, Deng and colleagues [140] in 2023 showed genetically predicted coffee consumption to be inversely related to CRC risk. In 2024, Liu and colleagues [141] investigated the causal associations between cutaneous melanoma and several lifestyle factors including coffee consumption (38 SNPs) and

Table 1 Mendelian randomization studies of coffee consumption and cancer

Author, year of publication	Design and sample	Results	Interpretation	Limitations reported
Skin cancer				
Ong, 2019	-35 SNPs for coffee intake -Logistic regression -UK Biobank (46,531 cancer cases, 270,342 controls)	MR estimate for UK Biobank (OR = 1.08, 95% CI, 0.91–1.28) per one cup/day increase in coffee consumption	No evidence supporting a causal relationship between coffee consumption and melanoma	Overlapping samples in UK Biobank; genetic instruments not specific for consumption; low statistical power
Carter, 2022	-12 SNPs for coffee consumption -Inverse variance weighted -UK Biobank (367,643 participants, 59,647 cases) FinnGen (218,792 participants)	MR estimate with adjustment for BMI and smoking initiation (OR = 1.03, 95% CI, 0.73–1.44)	No evidence supporting a causal relationship between coffee consumption and melanoma	Results only generalizable to European descent; weak instrument bias; possibility of low power; inability to evaluate linearity
Liu, 2024	-38 SNPs for coffee consumption -Inverse variance weighted -Sample (428,860 participants); 30,134 cases and 81,415 controls	MR estimate (OR = 0.827, 95% CI, 0.609–1.124)	No evidence supporting a causal relationship between coffee consumption and cutaneous melanoma	Results only generalizable to European descent; pleiotropy
CNS cancer				
Carter, 2022	-12 SNPs for coffee consumption -Inverse variance weighted -UK Biobank (367,643 participants, 59,647 cases) FinnGen (218,792 participants)	MR estimate with adjustment for BMI and smoking initiation (OR = 0.86, 95% CI, 0.32–2.30)	No evidence supporting a causal relationship between coffee consumption and brain cancer	Results only generalizable to European descent; weak instrument bias; possibility of low power; inability to evaluate linearity
Head and neck cancer				
Carter, 2022	-12 SNPs for coffee consumption -Inverse variance weighted -UK Biobank (367,643 participants, 59,647 cases) FinnGen (218,792 participants)	MR estimate with adjustment for BMI and smoking initiation (OR = 1.00, 95% CI, 0.57–1.74)	No evidence supporting a causal relationship	Results only generalizable to European descent; weak instrument bias; possibility of low power; inability to evaluate linearity
Thyroid cancer				
Carter, 2022	-12 SNPs for coffee consumption -Inverse variance weighted -UK Biobank (367,643 participants, 59,647 cases) FinnGen (218,792 participants)	MR estimate with adjustment for BMI and smoking initiation (OR = 1.43, 95% CI, 0.41–5.06)	No evidence of a causal association	Results only generalizable to European descent; weak instrument bias; possibility of low power; inability to evaluate linearity
Breast cancer				

Table 1 (continued)

Author, year of publication	Design and sample	Results	Interpretation	Limitations reported
Ong, 2019	-35 SNPs for coffee intake -Logistic regression -UK Biobank (46,531 cancer cases, 270,342 controls) -Meta-analysis of MR estimate of UK Biobank and publicly available summary data	MR estimate for UK Biobank (OR = 1.04, 95% CI, 0.94–1.14) per one cup/day increase in coffee consumption MR estimate for UK Biobank and publicly available summary data combined (OR = 1.00, 95% CI, 0.92–1.07) per one cup/day increase in coffee consumption	No evidence supporting a causal relationship between coffee consumption and breast cancer	Overlapping samples in UK Biobank; genetic instruments not specific for consumption; low statistical power
Ellingjord-Dale, 2021	-33 SNPs for coffee intake -Two-sample MR -UK Biobank (212,119 participants) -Breast Cancer Association Consortium (122,977 cases)	Causal ORs: Total breast cancer: (OR = 0.91, 95% CI, 0.80–1.02) ER-positive breast cancer: (OR = 0.90, 95% CI, 0.79–1.02) ER-negative breast cancer: (OR = 0.88, 95% CI, 0.75–1.03)	No evidence supporting a causal relationship between coffee consumption and breast cancer	Possibility of low statistical power; potential existence of non-linear associations could not be evaluated
Carter, 2022	-12 SNPs for coffee consumption -Inverse variance weighted -UK Biobank (367,643 participants, 59,647 cases) FinnGen (218,792 participants)	MR estimate with adjustment for BMI and smoking initiation (OR = 1.10, 95% CI, 0.87–1.39)	No evidence of a causal association	Results only generalizable to European descent; weak instrument bias; possibility of low power; inability to evaluate linearity
Lung cancer				
Ong, 2019	-35 SNPs for coffee intake -Logistic regression -UK Biobank (46,531 cancer cases, 270,342 controls) -Meta-analysis of MR estimate of UK Biobank and publicly available summary data	MR estimate for UK Biobank (OR = 1.08, 95% CI, 0.86–1.35) per one cup/day increase in coffee consumption MR estimate for UK Biobank and publicly available summary data combined (OR = 1.07, 95% CI, 0.93–1.23) per one cup/day increase in coffee consumption	No strong evidence supporting a causal relationship between coffee consumption and lung cancer	Overlapping samples in UK Biobank; genetic instruments not specific for consumption; low statistical power
Carter, 2022	-12 SNPs for coffee consumption -Inverse variance weighted -UK Biobank (367,643 participants, 59,647 cases) FinnGen (218,792 participants)	MR estimate with adjustment for BMI and smoking initiation (OR = 0.98, 95% CI, 0.67–1.44)	No evidence supporting a causal relationship	Results only generalizable to European descent; weak instrument bias; possibility of low power; inability to evaluate linearity
Esophageal cancer				

Table 1 (continued)

Author, year of publication	Design and sample	Results	Interpretation	Limitations reported
Carter, 2022	-12 SNPs for coffee consumption -Inverse variance weighted -UK Biobank (367,643 participants, 59,647 cases) FinnGen (218,792 participants)	MR estimate with adjustment for BMI and smoking initiation UK Biobank: (OR = 4.56, 95% CI, 2.26–9.21) FinnGen: (OR = 1.09, 95% CI, 0.21–5.77)	**Causal association between coffee consumption and increased risk of esophageal cancer**	Results only generalizable to European descent; weak instrument bias; possibility of low power; inability to evaluate linearity
Cai, 2024	-BioBank Japan (17,572 digestive system cancer cases and 195,745 controls) GWAS summary statistics (1300 cases and 195,745 controls)	(OR = 1.51, 95% CI, 0.78–2.91)	No evidence of a causal association	Results only generalizable to Eastern Asian participants; weak instrument bias; possibility of low power
Liver cancer				
Deng, 2022	-6 SNPs for coffee consumption -Inverse variance weighted -BioBank Japaan (152,634 participants)	MR estimate for HCC: (OR = 0.69; 95% CI, 0.53–0.90)	**Causal association between coffee consumption and reduced risk of HCC**	Low statistical power; results only generalizable to East Asians
Carter, 2022	-12 SNPs for coffee consumption -Inverse variance weighted -UK Biobank (367,643 participants, 59,647 cases) FinnGen (218,792 participants)	MR estimate with adjustment for BMI and smoking initiation (OR = 2.05, 95% CI, 0.63–6.67)	No evidence of a causal association	Results only generalizable to European descent; weak instrument bias; possibility of low power; inability to evaluate linearity
Cai, 2024	-BioBank Japan (17,572 digestive system cancer cases and 195,745 controls) -GWAS summary statistics (1866 cases and 195,745 controls)	(OR = 0.69, 95% CI, 0.53–0.90)	**Causal association between coffee consumption and reduced risk of HCC**	Results only generalizable to Eastern Asian participants; weak instrument bias; possibility of low power
Biliary tract cancer				
Carter, 2022	-12 SNPs for coffee consumption -Inverse variance weighted -UK Biobank (367,643 participants, 59,647 cases) FinnGen (218,792 participants)	MR estimate with adjustment for BMI and smoking initiation (OR = 1.28, 95% CI, 0.41–3.94)	No evidence of a causal association	Results only generalizable to European descent; weak instrument bias; possibility of low power; inability to evaluate linearity
Cai, 2024	-BioBank Japan (17,572 digestive system cancer cases and 195,745 controls) -GWAS summary statistics (339 cases and 195,745 controls)	(OR = 0.99, 95% CI, 0.66–1.49)	No evidence of a causal association	Results only generalizable to Eastern Asian participants; weak instrument bias; possibility of low power
Pancreatic cancer				

Table 1 (continued)

Author, year of publication	Design and sample	Results	Interpretation	Limitations reported
Carter, 2022	-12 SNPs for coffee consumption -Inverse variance weighted -UK Biobank (367,643 participants, 59,647 cases) FinnGen (218,792 participants)	MR estimate with adjustment for BMI and smoking initiation (OR = 1.44, 95% CI, 0.80–2.59)	No evidence of a causal association	Results only generalizable to European descent; weak instrument bias; possibility of low power; inability to evaluate linearity
Cai, 2024	-BioBank Japan (17,572 digestive system cancer cases and 195,745 controls) -GWAS summary statistics (442 cases and 195,745 controls)	(OR = 0.91, 95% CI, 0.66–1.26)	No evidence of a causal association	Results only generalizable to Eastern Asian participants; weak instrument bias; possibility of low power
Stomach cancer				
Carter, 2022	-12 SNPs for coffee consumption -Inverse variance weighted -UK Biobank (367,643 participants, 59,647 cases) FinnGen (218,792 participants)	MR estimate with adjustment for BMI and smoking initiation (OR = 1.16, 95% CI, 0.53–2.54)	No evidence of a causal association	Results only generalizable to European descent; weak instrument bias; possibility of low power; inability to evaluate linearity
Tan, 2023	-50 SNPS for East Asians and 119 SNPs for European populations -Inverse variance weighted -34,652 subjects of East Asian descent (6,563 cases and 195,745 controls)	Eastern Asia: (OR = 0.99, 95% CI, 0.93–1.04) European population: (OR = 1.27, 95% CI, 0.86–1.87)	No evidence of a causal association	Possibility of low power; pleiotropy
Cai, 2024	-BioBank Japan (17,572 digestive system cancer cases and 195,745 controls) -GWAS summary statistics (6563 cases and 195,745 controls)	(OR = 1.12, 95% CI, 0.96–1.30)	No evidence of a causal association	Results only generalizable to Eastern Asian participants; weak instrument bias; possibility of low power
Colorectal cancer				
Ong, 2019	-35 SNPs for coffee intake -Logistic regression -UK Biobank (46,531 cancer cases, 270,342 controls)	MR estimate for UK Biobank (OR = 1.43, 95% CI, 1.22–1.67) per one cup/day increase in coffee consumption	No evidence supporting a causal relationship between coffee consumption and colorectal cancer	Overlapping samples in UK Biobank; genetic instruments not specific for consumption; low statistical power
Carter, 2022	-12 SNPs for coffee consumption -Inverse variance weighted -UK Biobank (367,643 participants, 59,647 cases) FinnGen (218,792 participants)	MR estimate with adjustment for BMI and smoking initiation (OR = 1.06, 95% CI, 0.77–1.46)	No evidence of a causal association	Results only generalizable to European descent; weak instrument bias; possibility of low power; inability to evaluate linearity

Table 1 (continued)

Author, year of publication	Design and sample	Results	Interpretation	Limitations reported
Deng, 2023	-6 SNPs for coffee consumption -Inverse variance weighted BioBank Japaan (152,634 participants)	MR estimate for HCC: (OR = 0.80; 95% CI, 0.64–0.99) per one-unit change	**Causal association between coffee consumption and reduced risk of colorectal cancer**	Low statistical power; weak instrument bias; results only generalizable to East Asians
He, 2024	-5–91 SNPs -Inverse variance weighted UK Biobank (250,308 participants)	Decaffeinated coffee: (OR = 1.025, 95% CI, 0.995–1.005) Ground coffee: (OR = 0.994, 95% CI, 0.983–1.005) Instant coffee (OR = 0.994, 95% CI, 0.978–1.010) Other coffee: (OR = 1.000, 95% CI, 0.869–1.150)	No evidence of a causal association	Results only generalizable to European descent; possibility of low statistical power
Cai, 2024	-BioBank Japan (17,572 digestive system cancer cases and 195,745 controls) -GWAS summary statistics (7062 cases and 195,745 controls),	(OR = 1.04, 95% CI, 0.88–1.21)	No evidence of a causal association	Results only generalizable to Eastern Asian participants; weak instrument bias; possibility of low power
Kidney cancer				
Ong, 2019	-35 SNPs for coffee intake -Logistic regression -UK Biobank (46,531 cancer cases, 270,342 controls)	MR estimate for UK Biobank (OR = 0.90, 95% CI, 0.67–1.20) per one cup/day increase in coffee consumption	No evidence supporting a causal relationship between coffee consumption and kidney cancer	Overlapping samples in UK Biobank; genetic instruments not specific for consumption; low statistical power
Carter, 2022	-12 SNPs for coffee consumption -Inverse variance weighted -UK Biobank (367,643 participants, 59,647 cases) FinnGen (218,792 participants)	MR estimate with adjustment for BMI and smoking initiation (OR = 0.86, 95% CI, 0.48–1.56)	No evidence supporting a causal relationship	Results only generalizable to European descent; weak instrument bias; possibility of low power; inability to evaluate linearity
Bladder cancer				
Carter, 2022	-12 SNPs for coffee consumption -Inverse variance weighted -UK Biobank (367,643 participants, 59,647 cases) FinnGen (218,792 participants)	MR estimate with adjustment for BMI and smoking initiation (OR = 1.07, 95% CI, 0.70–1.65)	No evidence of a causal association	Results only generalizable to European descent; weak instrument bias; possibility of low power; inability to evaluate linearity
Deng, 2022	-12 SNPs for coffee consumption -Inverse variance weighted -UK Biobank (420,838 participants) FinnGen (175,121 participants)	MR estimates UK Biobank: (OR = 1.02, 95% CI, 0.68–0.54) FinnGen: (OR = 0.89, 95% CI, 0.47–1.70)	No evidence of a causal association	Results only generalizable to European descent;; possibility of low power; inability to evaluate linearity

Table 1 (continued)

Author, year of publication	Design and sample	Results	Interpretation	Limitations reported
Prostate cancer				
Taylor, 2017	-2 SNPs for caffeine intake -Logistic regression -25 studies from PRACTICAL consortium (46,687 men of European ancestry)	Genetic risk score (combining 2 variants) and prostate cancer risk (OR = 1.01, 95% CI, 0.98–1.03), high-grade compared with low-grade disease (OR = 1.03, 95% CI, 0.97–1.04), and prostate-cancer mortality (HR = 1.03, 95% CI, 0.98–1.08) per additional coffee increasing allele	No evidence supporting a causal relationship between coffee consumption and prostate cancer incidence or progression	Heterogeneity between studies; genetic instruments not specific for coffee consumption; pleiotropy; possibility of low statistical power
Ong, 2019	-35 SNPs for coffee intake -Logistic regression -UK Biobank (46,531 cancer cases, 270,342 controls) -Meta-analysis of MR estimate of UK Biobank and publicly available summary data	MR estimate for UK Biobank (OR = 0.86, 95% CI, 0.76–0.98) per one cup/day increase in coffee consumption MR estimate for UK Biobank and publicly available summary data combined (OR = 0.91, 95% CI, 0.83–0.99) per one cup/day increase in coffee consumption	**Minor protective effect of coffee consumption on prostate cancer risk**	Overlapping samples in UK Biobank; genetic instruments not specific for consumption; low statistical power
Wang, 2021	-Use of primary and secondary genetic instruments -Inverse variance weighted -PRACTICAL (79,194 cases and 61,112 controls) and FinnGen project (4754 cases and 63,465 controls)	MR estimates: Primary genetic instruments PRACTICAL: (OR = 1.001, 95% CI, 0.997–1.005) FinnGen: (OR = 1.005, 95% CI, 0.998–1.012) Secondary genetic instruments PRACTICAL: (OR = 1.05, 95% CI, 0.93–1.18) FinnGen: (OR = 1.19, 95% CI, 0.92–1.54)	No evidence supporting a causal relationship between coffee consumption and prostate cancer risk	Possibility of low statistical power
Carter, 2022	-12 SNPs for coffee consumption -Inverse variance weighted -UK Biobank (367,643 participants, 59,647 cases) FinnGen (218,792 participants)	MR estimate with adjustment for BMI and smoking initiation (OR = 0.83, 95% CI, 0.65–1.07)	No evidence of a causal association	Results only generalizable to European descent; weak instrument bias; possibility of low power; inability to evaluate linearity
Testicular cancer				

Table 1 (continued)

Author, year of publication	Design and sample	Results	Interpretation	Limitations reported
Carter, 2022	-12 SNPs for coffee consumption -Inverse variance weighted -UK Biobank (367,643 participants, 59,647 cases) FinnGen (218,792 participants)	MR estimate with adjustment for BMI and smoking initiation (OR = 0.93, 95% CI, 0.29–2.97)	No evidence of a causal association	Results only generalizable to European descent; weak instrument bias; possibility of low power; inability to evaluate linearity
Cervical cancer				
Carter, 2022	-12 SNPs for coffee consumption -Inverse variance weighted -UK Biobank (367,643 participants, 59,647 cases) FinnGen (218,792 participants)	MR estimate with adjustment for BMI and smoking initiation (OR = 1.20, 95% CI, 0.69–2.09)	No evidence of a causal association	Results only generalizable to European descent; weak instrument bias; possibility of low power; inability to evaluate linearity
Ovarian cancer				
Ong, 2018	-4 SNPs for coffee consumption and 2 SNPs for caffeine intake -Two-sample MR -Ovarian Cancer Association Consortium (44,062 individuals of European ancestry)	Causal ORs for coffee consumption and cancers Epithelial ovarian cancer (EOC): 0.92 (0.79–1.06) High-grade serous EOC: 0.90 (0.73–1.10) Per one additional cup/day Causal ORs for caffeine intake and cancers Epithelial ovarian cancer (EOC): 1.01 (0.92–1.11) High-grade serous EOC: 0.90 (0.73–1.10) Per additional 80 mg caffeine	No evidence indicative of a strong association between genetically predicted coffee or caffeine levels and epithelial ovarian cancer risk	Results less generalizable to populations of non-European ancestry; SNPs accounted for only a small proportion of variation; low statistical power
Ong, 2019	-35 SNPs for coffee intake -Logistic regression -UK Biobank (46,531 cancer cases, 270,342 controls) -Meta-analysis of MR estimate of UK Biobank and publicly available summary data	MR estimate for UK Biobank (OR = 0.82, 95% CI, 0.67–1.00) per one cup/day increase in coffee consumption MR estimate for UK Biobank and publicly available summary data combined (OR = 0.88, 95% CI, 0.78–0.99) per one cup/day increase in coffee consumption	**Minor protective effect of coffee consumption on ovarian cancer risk**	Overlapping samples in UK Biobank; genetic instruments not specific for consumption; low statistical power

Table 1 (continued)

Author, year of publication	Design and sample	Results	Interpretation	Limitations reported
Carter, 2022	-12 SNPs for coffee consumption -Inverse variance weighted -UK Biobank (367,643 participants, 59,647 cases) FinnGen (218,792 participants)	MR estimate with adjustment for BMI and smoking initiation FinnGen: (OR = 1.03, 95% CI, 0.39–2.75) UK Biobank: (OR = 0.55, 95% CI, 0.31–0.98)	No evidence of a causal association	Results only generalizable to European descent; weak instrument bias; possibility of low power; inability to evaluate linearity
Liu, 2023	-36 SNPs for coffee consumption -Inverse variance weighted -Ovarian Cancer Association Consortium	Ovarian cancer: (OR = 1.40, 95% CI, 1.02–1.93) Endometroid ovarian cancer: (OR = 3.01, 95% CI, 1.50–6.04) per 50% increase	**Causal association between coffee consumption and increased risk of overall ovarian and endometroid ovarian cancer**	Results only generalizable to European descent; pleiotropy
Endometrial cancer				
Ong, 2019	-35 SNPs for coffee intake -Logistic regression -UK Biobank (46,531 cancer cases, 270,342 controls)	MR estimate for UK Biobank (OR = 1.07, 95% CI, 0.88–1.31) per one cup/day increase in coffee consumption	No evidence supporting a causal relationship between coffee consumption and endometrial cancer	Overlapping samples in UK Biobank; genetic instruments not specific for consumption; low statistical power
Carter, 2022	-12 SNPs for coffee consumption -Inverse variance weighted -UK Biobank (367,643 participants, 59,647 cases) FinnGen (218,792 participants)	MR estimate with adjustment for BMI and smoking initiation (OR = 1.02, 95% CI, 0.61–1.71)	No evidence of a causal association	Results only generalizable to European descent; weak instrument bias; possibility of low power; inability to evaluate linearity
Chen, 2023	-12 SNPs for coffee consumption and 2 for caffeine intake -Inverse variance weighted -EC Association Consortium, ECAC (12,906 cases and 108,979 controls) FinnGen (1,967 cases and 167,189 controls)	Coffee consumption ECAC: (OR = 1.22, 95% CI, 0.69–2.14) FinnGen: (OR = 1.74, 95% CI, 0.59–5.14) Caffeine consumption ECAC: (OR = 0.85, 95% CI, 0.72–1.00) FinnGen: (OR = 1.20, 95% CI, 0.26–5.59)	No evidence of a causal association between coffee or caffeine consumption and endometrial cancer	Pleiotropy; results only generalizable to European descent;
Hematological cancers				
Ong, 2019	-35 SNPs for coffee intake -Logistic regression -UK Biobank (46,531 cancer cases, 270,342 controls)	MR estimate for UK Biobank (OR = 1.21, 95% CI, 1.00–1.47) per one cup/day increase in coffee consumption	No evidence supporting a causal relationship between coffee consumption and lymphoma	Overlapping samples in UK Biobank; genetic instruments not specific for consumption; low statistical power

Table 1 (continued)

Author, year of publication	Design and sample	Results	Interpretation	Limitations reported
Carter, 2022	-12 SNPs for coffee consumption -Inverse variance weighted -UK Biobank (367,643 participants, 59,647 cases) FinnGen (218,792 participants)	MR estimate with adjustment for BMI and smoking initiation UK Biobank: (OR = 3.45, 95% CI, 1.54–7.73) FinnGen: (OR = 0.86, 95% CI, 0.30–2.44)	**Causal association between coffee consumption and increased risk of multiple myeloma**	Results only generalizable to European descent; weak instrument bias; possibility of low power; inability to evaluate linearity
Carter, 2022	-12 SNPs for coffee consumption -Inverse variance weighted -UK Biobank (367,643 participants, 59,647 cases) FinnGen (218,792 participants)	MR estimate with adjustment for BMI and smoking initiation (OR = 1.30, 95% CI, 0.82–2.06)	No evidence of a causal association between coffee consumption and non-Hodgkin lymphoma	Results only generalizable to European descent; weak instrument bias; possibility of low power; inability to evaluate linearity
Carter, 2022	-12 SNPs for coffee consumption -Inverse variance weighted -UK Biobank (367,643 participants, 59,647 cases) FinnGen (218,792 participants)	MR estimate with adjustment for BMI and smoking initiation (OR = 0.66, 95% CI, 0.37–1.17)	No evidence of a causal association between coffee consumption and leukaemia	Results only generalizable to European descent; weak instrument bias; possibility of low power; inability to evaluate linearity
Overall cancer incidence and mortality				
Ong, 2019	-35 SNPs for coffee intake -Logistic regression -UK Biobank (46,531 cancer cases, 270,342 controls)	MR estimate for UK Biobank Overall cancer incidence: (OR = 1.01, 95% CI, 0.94–1.08) per one cup/day increase in coffee consumption Overall cancer mortality: (OR = 1.11, 95% CI, 0.95–1.31) per one cup/day increase in coffee consumption	No evidence supporting a causal relationship between coffee consumption and overall cancer incidence and mortality	Overlapping samples in UK Biobank; genetic instruments not specific for consumption; low statistical power
Carter, 2022	-12 SNPs for coffee consumption -Inverse variance weighted -UK Biobank (367,643 participants, 59,647 cases) FinnGen (218,792 participants)	MR estimate with adjustment for BMI and smoking initiation (OR = 1.06, 95% CI, 0.95–1.18)	No evidence of a causal association between coffee consumption and any cancer	Results only generalizable to European descent; weak instrument bias; possibility of low power; inability to evaluate linearity

BMI body mass index, *CI* confidence interval, *GWAS* genome-wide association study, *HCC* hepatocellular cancer, *MR* Mendelian randomization, *OR* odds ratio, *SNPs* single-nucleotide polymorphisms

reported no significant evidence of a causal association between coffee consumption and cutaneous melanoma. Chen and colleagues [142] in 2023 used 12 and 2 independent variants associated with coffee and caffeine consumption, respectively, and showed no strong evidence that coffee and caffeine consumption was causally related to endometrial cancer or its prognosis. Using 36 variants for coffee consumption and data from the Ovarian Cancer Association Consortium, Liu and colleagues [143] in 2023 showed that genetically predicted coffee consumption was associated with an increased risk of overall ovarian cancer and endometroid ovarian cancer. Tan and colleagues [144] in 2023 evaluated the associations between lifestyle habits including coffee intake with gastric cancer in an East Asian population and found no evidence of a causal relationship between coffee intake and gastric cancer. Using summary-level GWAS data from the UK Biobank and data on CRC cases and controls, He and colleagues [145] in 2024 reported no conclusive evidence supporting a causal relationship between coffee consumption and CRC risk. In 2024, Cai and colleagues [146] explored the associations between coffee consumption and digestive system cancers including esophageal, gastric, colorectal, hepatocellular, biliary tract, and pancreatic cancer in East Asian populations. Their results showed that coffee consumption had a potential protective effect on HCC, with no strong evidence of an effect on other cancers [146].

Overall, MR studies on coffee consumption and cancer risk have yielded mixed findings. Generally, these studies do not provide strong evidence supporting causal relationships between genetically predicted coffee or caffeine consumption and most cancers. Despite this, some MR studies suggest potential protective effects of coffee on hepatocellular and colorectal cancers, with weak protective effects observed for prostate cancer. However, apart from HCC, these findings are based on single studies. The findings on ovarian cancer risk are inconsistent, showing both protective and increased risk associations. Additionally, single MR studies reported an increased risk of esophageal cancer and multiple myeloma with coffee consumption.

It is important to note, however, that while MR studies offer a powerful tool for assessing causal relationships by using genetic variants as instrumental variables, they are not without limitations and potential sources of bias. One key limitation is the assumption that the genetic variants used as instruments are exclusively associated with the exposure of interest (in this case, coffee consumption) and not with any confounders—a principle known as the "exclusion restriction criterion." Violations of this assumption, such as pleiotropy, where a genetic variant influences multiple traits, can lead to biased results. Additionally, MR studies rely on the accuracy and robustness of the genetic instruments; if the variants are weakly associated with the exposure, the study may suffer from weak instrument bias, leading to unreliable estimates. Population stratification is another potential source of bias, as differences in allele frequencies across populations can confound results if not properly accounted for, especially in studies involving diverse ethnic groups. Furthermore, MR studies typically assume a linear relationship between the genetic instrument and the exposure, which may not hold true in complex biological systems. The interpretation of MR results can also be complicated by the possibility of reverse causation, where the disease process influences the exposure level, although MR is specifically designed to mitigate this issue in observational studies. Finally, MR studies often provide insights into average effects across populations, which might not capture the nuances of individual variability in response to coffee consumption.

Potential pathways underlying the associations between coffee consumption, its bioactive components, and cancer outcomes

The review of longitudinal observational studies found that coffee consumption was generally associated with a lower risk of several cancers, including skin, liver, prostate, and endometrial cancers (Fig. 1). Additionally, coffee might reduce the risk of cancer recurrence, particularly in CRC. However, the evidence was not conclusive for many other cancers, including CNS, mouth, pharyngeal, laryngeal and esophageal cancers, breast cancer, and pancreatic cancer, among others. Notably, coffee consumption was consistently associated with an increased risk of lung cancer. Results of MR studies were mixed, generally not supporting a strong causal relationship for most cancers, though some

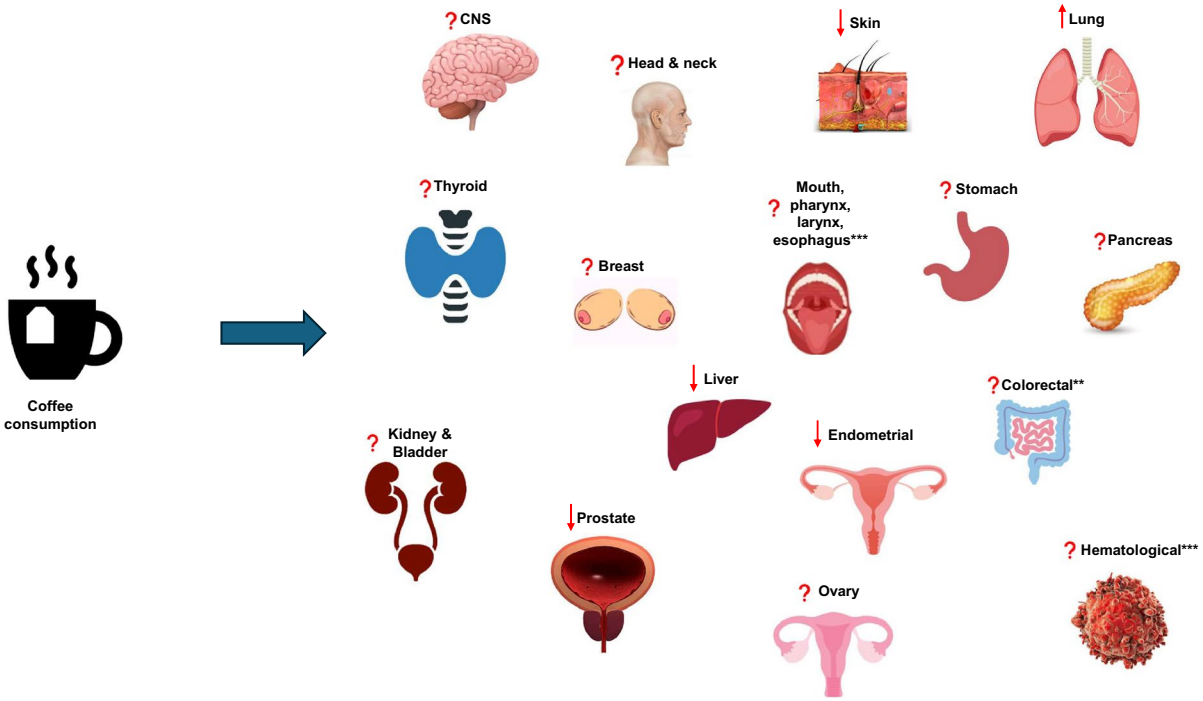

Fig. 1 Coffee consumption and cancer outcomes: summary of effects based on large-scale longitudinal observational studies. CNS, central nervous system; hematological cancers include leukemia, multiple myeloma and the lymphomas. ↓, decreased risk; ↑, increased risk; ?, inconclusive or limited evidence. **, single Mendelian randomization (MR) studies suggest a protective association. ***, single MR studies suggest an increased risk of esophageal cancer and multiple myeloma with coffee consumption. The protective effects of coffee consumption on liver and prostate cancer were confirmed by both observational and MR studies

suggest potential protective effects for hepatocellular, colorectal, and possibly prostate cancers, with an increased risk for esophageal cancer and multiple myeloma. The relationship between coffee consumption and cancer outcomes is complex and multifactorial. The inconsistency in the findings for certain site-specific cancers may stem from several factors. These include differences in study populations, which can vary widely in age, sex, race, and genetic backgrounds. Additionally, study design elements such as sample size, follow-up duration, and the extent of adjustment for confounding variables also play relevant roles. Smaller sample sizes or shorter follow-up periods may not adequately capture the relationships between coffee consumption and cancer outcomes. Moreover, studies that do not sufficiently adjust for confounders might report associations that could be attributed to these uncontrolled variables rather than to coffee consumption itself. Importantly, various cancers have different etiologies and mechanistic pathways underlying their development.

Coffee is a complex beverage containing numerous bioactive components that could potentially influence cancer risk and progression. Some of the key bioactive components include caffeine, chlorogenic acids, diterpenes (such as cafestol and kahweol), and various antioxidants [25]. Several pathways have been proposed for the protective effects of coffee and its bioactive components on some cancers (Fig. 2). Chronic inflammation and oxidative stress are common pathways in the development of many cancers [147]. Coffee's bioactive compounds, particularly antioxidants, can reduce oxidative stress and inflammation [30], thereby lowering cancer risk.

Caffeine, a major bioactive compound in coffee, is known for its stimulating effects on the CNS [31]. It also has antioxidant properties that can protect cells from oxidative damage. Caffeine has been shown to exert significant transcriptomic effects in vitro on

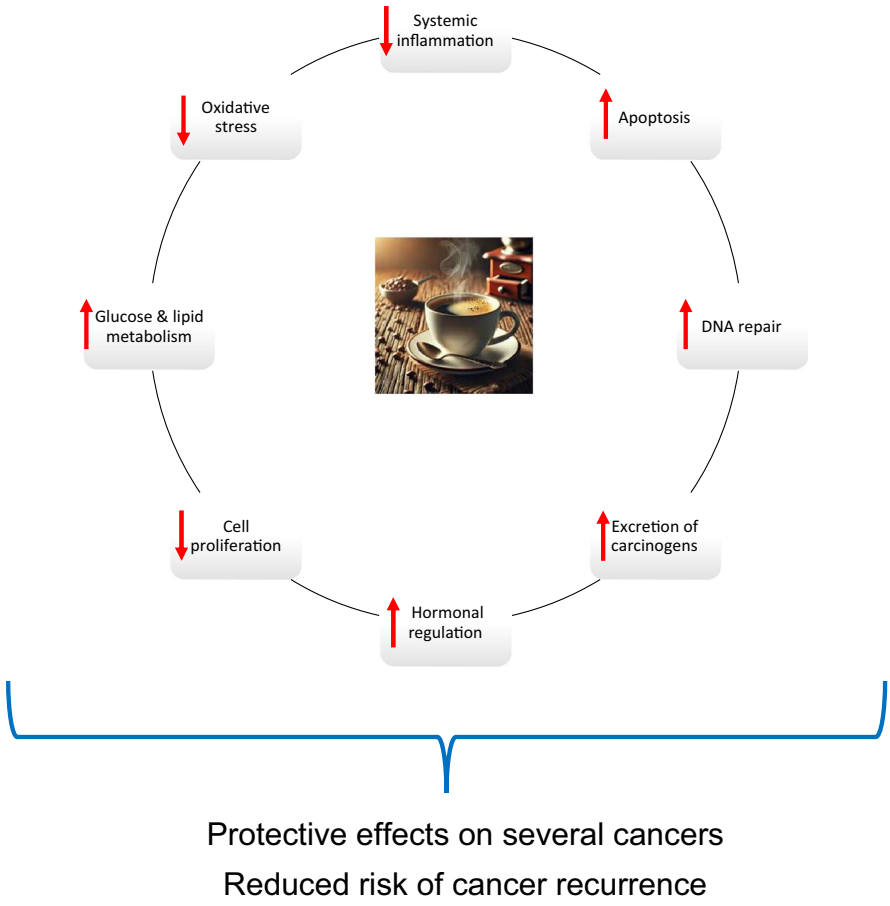

Fig. 2 Proposed mechanistic pathways underlying the protective effects of coffee consumption and its bioactive compounds on cancer outcomes and recurrence. Coffee consumption may help extend healthspan and promote longevity based on its protective effects on several cancers, ability to reduce cancer recurrence and through its beneficial effects on fundamental biological processes involved in aging

various cell types relevant to cancer research, including epithelial cells, fibroblasts, and cancer stem cells [148–150]. Transcriptomic analyses reveal that caffeine modulates the expression of a wide array of genes involved in critical cellular processes such as apoptosis, cell cycle regulation, DNA repair, inflammation, and oxidative stress response [148, 151]. Notably, caffeine has been found to upregulate the expression of tumor suppressor genes, such as p53, and downregulate oncogenes, such as MYC, in several cancer cell lines [152]. This modulation of gene expression can induce cell cycle arrest and promote apoptosis, thereby inhibiting cancer cell proliferation. Indeed, caffeine has been shown to inhibit the growth of cancer cells and induce apoptosis in various cancer cell lines [151, 153, 154]. Additionally, caffeine has been shown to enhance the DNA damage response by upregulating genes involved in nucleotide excision repair and homologous recombination, which may prevent the accumulation of mutations that drive cancer progression [149, 150, 155–160]. Studies suggest that caffeine may reduce the risk of skin cancer by enhancing DNA repair and reducing UVB-induced skin damage [154, 161]. Research indicates that caffeine can inhibit UVB-induced formation of thymine dimers and enhance UVB-induced apoptosis in both neoplasms and UV-damaged keratinocytes [162]. Additionally, caffeine's ability to override the DNA damage-induced cell cycle arrest can lead to increased cell death in damaged cells, thereby potentially reducing the risk of skin cancer. Furthermore, caffeine may reduce the expression of genes associated with the epithelial-to-mesenchymal transition (EMT) [163–165], a process linked to cancer metastasis, thereby potentially limiting the invasiveness of cancer cells. Caffeine also alters production of extracellular matrix components, which may also protect against metastasis formation [166]. These findings

suggest that caffeine's transcriptomic effects may contribute to its observed anti-cancer properties, providing a molecular basis for its potential role in cancer prevention and therapy. However, while these in vitro studies offer promising insights, further research is needed to validate these effects in vivo and to understand their implications in the context of human cancer [151].

Chlorogenic acids are polyphenolic compounds abundant in coffee and possess strong antioxidant and anti-inflammatory properties [30]. Chlorogenic acids have also been found to modulate glucose and lipid metabolism [167, 168], potentially influencing cancer risk through metabolic pathways. Glucose and lipid metabolism are important factors in cancer development [169]. Improved insulin sensitivity and lower blood sugar levels associated with coffee consumption [13] may reduce the risk of cancers linked to the metabolic syndrome, such as liver and colorectal cancers. Additionally, chlorogenic acids exhibit antitumour properties by arresting cell proliferation, promoting apoptosis, and facilitating intracellular DNA impairment [168, 170]. Cafestol and kahweol are diterpenes which are present in unfiltered coffee and have been shown to have anti-inflammatory and anticarcinogenic properties [26]. Diterpenes can induce phase II detoxifying enzymes, enhance the excretion of carcinogens, induce apoptosis, and inhibit cancer cell proliferation and tumor metastasis [26]. These two coffee diterpenes have also been shown to work synergistically with several anti-cancer drugs [171]. However, they also raise cholesterol levels, which could potentially counteract their beneficial effects in some individuals.

Coffee is a rich source of antioxidants, which can neutralize free radicals and reduce oxidative damage to cells. This antioxidant activity is necessary for preventing DNA mutations that could lead to cancer. Coffee or caffeine consumption has been associated with changes in circulating hormone levels, such as sex hormone binding globulin, estrogen, C-peptide, and adiponectin [172–176]; coffee has been reported to lower levels of estrogen [177]. This is particularly relevant for hormone-related cancers, such as breast and endometrial cancers, where hormonal regulation plays a significant role in cancer development and progression. The protective effects of coffee consumption on cancer recurrence are primarily attributed to its bioactive compounds via the pathways described above which include antioxidant activities, anti-inflammatory effects, regulation of metabolism, apoptosis, and cell cycle regulation.

The potential pathways underlying the association between coffee consumption and an increased risk of lung cancer could be multifaceted. First, residual confounding by smoking is a major factor since smokers are more likely to consume coffee. This confounding can skew results even when adjustments are made in studies. However, this explanation did not appear to be the reason for studies that accounted for smoking. Jin and Je [49] in their 2024 meta-analysis showed that the association between coffee consumption and lung cancer was attenuated in a pooled analysis of studies that adjusted for BMI. Second, the type of coffee preparation, such as unfiltered coffee, which contains higher levels of carcinogenic diterpenes, might play a role. Additionally, genetic factors and differences in metabolism of coffee compounds might also influence individual susceptibility to lung cancer. The varying results across different studies highlight the need for further research to clarify these associations and understand the underlying biological mechanisms. More robust studies with larger sample sizes, longer follow-up periods, and better control of confounding factors are necessary to draw definitive conclusions.

Coffee consumption and healthy aging

Cancer is fundamentally an age-related disease, with its incidence increasing significantly as individuals grow older. The cellular and molecular mechanisms that drive the aging process [178]—such as genomic instability, telomere attrition, epigenetic alterations, and chronic inflammation—are central to the pathogenesis of cancer. These aging-related processes create a biological environment conducive to the development and progression of cancer, as well as other chronic diseases associated with aging. Interventions that optimize or decelerate the aging process have the potential to inhibit the genesis of all age-related diseases simultaneously, including cancer. By targeting the underlying mechanisms of aging, such interventions can reduce the risk of not only cancer but also other chronic conditions such as CVD, diabetes, and neurodegenerative disorders. Conversely, lifestyle factors that exacerbate one or more biological

mechanisms of aging—such as poor diet, physical inactivity, and smoking—accelerate the aging process. This accelerated aging is associated with an increased incidence of all age-related diseases, including various cancers. Given this understanding, preventive medicine and public health strategies must adopt a holistic approach that focuses on promoting healthy aging and optimizing the aging process. Complex strategies, including lifestyle interventions, are essential to achieving this goal. A healthy diet that exerts anti-aging effects is crucial in this context. Based on the available evidence, moderate coffee consumption can be considered a part of such a diet, contributing to the promotion of healthy aging. Lifestyle strategies that are commonly adopted to extend healthspan and promote longevity include the following: (i) consuming a balanced diet rich in fruits, vegetables, whole grains, lean proteins, and healthy fats; diets like the Mediterranean diet have been linked to longer healthspans [179]; (ii) regular exercise helps maintain a healthy weight, improves cardiovascular health, and reduces the risk of various chronic diseases [180–182]; (iii) refraining from smoking, limiting alcohol consumption, and avoiding exposure to environmental toxins [183] are important for reducing the risk of diseases; (iv) managing stress, maintaining social connections, and engaging in activities that promote mental well-being contribute to a longer, healthier life [184]; (v) early detection and management of health conditions through regular check-ups can prevent diseases from progressing. Coffee's bioactive compounds, including antioxidants and anti-inflammatory agents, may help mitigate some of the detrimental effects of aging [30], thereby reducing the risk of age-related diseases, including cancer. By incorporating moderate coffee consumption into a balanced diet, individuals may enhance their healthspan and potentially delay the onset of chronic diseases associated with aging. Our comprehensive review on coffee consumption and cardiometabolic health addresses these aspects [13].

In summary, while coffee consumption appears to offer several health benefits that can extend the healthspan and promote longevity, it is important to recognize that the evidence is not uniform across all cancer types. For instance, some studies have consistently linked coffee consumption to an increased risk of lung cancer, highlighting the complexity of coffee's effects on health. This underscores the need for further research to fully understand the impact of coffee on different cancers and overall health outcomes. Nonetheless, embracing a balanced approach that includes coffee consumption, a healthy diet, regular physical activity, and other positive lifestyle habits, remains one of the most effective strategies for promoting a long and healthy life.

Clinical and public health implications

The review's findings on coffee consumption and cancer outcomes may have several important clinical and public health implications. Observational evidence shows coffee consumption to be associated with a lower risk of specific cancers, including skin, liver, prostate, and endometrial cancers. Additionally, it may reduce the risk of cancer recurrence, particularly CRC. These inverse associations were generally consistent across different age and sex groups and geographical locations, and the protective effects were most pronounced with the consumption of three or more cups of coffee per day (albeit based on limited evidence). However, the evidence was not conclusive for several other cancers, and coffee consumption was consistently associated with an increased risk of lung cancer. The protective effect on liver and prostate cancer were confirmed by both observational and MR studies.

Clinicians should consider advising patients on the potential benefits of moderate coffee consumption as part of a comprehensive approach to healthy aging and cancer prevention. Moderate coffee consumption appears broadly beneficial; hence, specific recommendations for particular populations cannot be confidently made at this time. This guidance could be especially relevant for individuals at higher risk of developing skin, liver, prostate, and endometrial cancers. For patients in remission from colorectal cancer, incorporating coffee into their diet might be recommended to help reduce the risk of recurrence. Given the variability in cancer etiology, the differential effects of coffee consumption, and the complexity of the health effects of coffee, long-term public health strategies could focus on personalized recommendations. For example, patients with a history of smoking or those at higher risk of lung cancer should be cautioned about the increased risk associated with coffee consumption. Individual risk factors, such as

age, pre-existing health conditions, and genetic predispositions should also be taken into consideration. Clinicians must weigh the potential benefits against the risks and consider the patient's overall health status and risk factors. It is essential to educate patients about the potential protective effects of coffee, its adverse effects, and the importance of moderation, while also emphasizing that coffee consumption should complement, not replace, other preventive measures such as regular screenings, a balanced diet, and a healthy lifestyle.

From a public health perspective, authorities could consider including coffee consumption in dietary guidelines, highlighting its potential benefits in promoting healthy aging in general and in reducing the risk of certain cancers in particular. However, it is crucial that these guidelines also address the increased risk of lung cancer associated with coffee consumption, particularly among smokers. Public health campaigns can utilize these findings to promote coffee consumption as part of a healthy lifestyle, but with a balanced message that acknowledges both the benefits and the potential risks. Such campaigns can play a vital role in dispelling myths about coffee and emphasizing its role in cancer prevention. Policymakers could support initiatives that fund research on dietary factors and cancer prevention. Additionally, policies promoting access to healthy dietary options, including coffee, can be integrated into broader strategies for cancer prevention and health promotion.

The review suggests that the protective effects of coffee consumption do not significantly vary by age or sex, indicating that these recommendations could be broadly applicable. However, it is crucial to focus particular attention on populations at higher risk of lung cancer. Tailored public health messages and clinical advice should be designed to address the specific needs and risks of these groups to ensure effective and safe dietary recommendations.

Gaps and future research directions

While the existing body of research on coffee consumption and cancer outcomes has provided valuable insights, several gaps and areas for future research remain. Addressing these gaps is relevant for developing a comprehensive understanding of how coffee influences cancer risk and for providing clear guidance to the public. Most studies to date have relied on baseline assessments of coffee consumption, failing to account for changes in consumption over time. This limitation introduces the risk of regression dilution bias, where the true association between coffee consumption and cancer risk may be underestimated. While coffee consumption is one of the more stable dietary habits [185], future research should incorporate repeated assessments throughout the follow-up period to more accurately capture long-term exposure and its potential effects on cancer outcomes. The evidence regarding coffee consumption and its association with several types of cancer remains inconclusive. This includes cancers of the CNS, head and neck, breast, mouth, pharynx, larynx, esophagus, stomach, pancreas, bile duct, gall bladder, kidneys, bladder, ovaries, leukemia, myeloma, lymphoma, overall cancer incidence, and cancer mortality. For some of these cancers, most of the evidence was based on case–control designs which are limited by lack of temporality. To clarify these relationships, large-scale longitudinal studies with diverse populations and longer follow-up periods are needed. Such studies should aim to confirm or refute any protective or harmful associations observed in earlier research. Current research has not sufficiently explored how the effects of coffee consumption may vary across different subgroups of the population. It is important to understand how factors such as age, sex, race and ethnicity, BMI, and smoking status might influence the relationship between coffee and cancer risk. Identifying subgroups that may benefit more from coffee consumption or those at greater risk can help tailor public health recommendations and clinical advice. There is a need for detailed studies to investigate dose–response relationships between coffee consumption and cancer outcomes. Most studies just compared individuals with the highest versus lowest levels of consumption without assigning specific values. Future studies should aim to determine the specific quantities of coffee that are associated with protective effects for various cancers and the levels that may pose risks, particularly concerning lung cancer. Studies should also focus on understanding subgroup variations to provide more tailored dietary guidance. Understanding these dose–response curves is critical for developing evidence-based guidelines for safe and beneficial coffee consumption. Except for liver and prostate cancer, it is challenging to reconcile

the mixed results from MR studies and observational data. The findings from MR studies highlight gaps and future research directions in understanding the relationship between coffee consumption and cancer risk. First, the mixed and inconsistent results across different cancer types suggest a need for more comprehensive and targeted MR studies to clarify these associations. Common limitations of these MR studies included lack of reliable genetic instruments, low statistical power, pleiotropy, linkage disequilibrium, and collider bias, amongst many others [133]. Additionally, the potential protective and adverse effects observed for certain cancers, such as HCC, CRC, prostate cancer, esophageal cancer, and multiple myeloma, were mostly based on single studies and therefore require further validation through larger, well-powered studies. The biological mechanisms underlying these associations remain inadequately understood, necessitating detailed mechanistic studies to elucidate the pathways through which coffee consumption may influence cancer risk. These studies should explore the biological mechanisms underlying the beneficial effects observed for some cancers, such as the antioxidant, anti-inflammatory, and anti-carcinogenic properties of coffee's bioactive compounds. Additionally, it is important to investigate the mechanisms contributing to the increased risk of lung cancer associated with coffee consumption. Such research could reveal potential interactions between coffee components and other risk factors, such as smoking and BMI. In summary, addressing these research gaps will be essential for developing targeted dietary recommendations and public health strategies that maximize the benefits and minimize the risks of coffee consumption in different population groups.

Conclusions

The review on coffee consumption and cancer outcomes indicates both potential benefits and risks associated with coffee intake. Coffee consumption is linked to a reduced risk of several cancers, including skin, liver, prostate, and endometrial cancers, with the strongest protective effects observed at consumption levels of three or more cups per day. Additionally, coffee may lower the risk of cancer recurrence, particularly in colorectal cancer, and these benefits appear to be consistent across various age and sex groups. However, the evidence remains inconclusive for many other cancers, including those of the CNS, head and neck, breast, and gastrointestinal tract. Importantly, coffee consumption has been consistently associated with an increased risk of lung cancer, which underscores the need for careful consideration of individual health profiles when making dietary recommendations.

Mendelian randomization studies have generally not supported strong causal links between coffee consumption and most cancers, with the exception of liver and prostate cancer, where protective effects were observed in both observational and MR studies. Clinically, these findings suggest that moderate coffee consumption could be incorporated into cancer prevention strategies for specific cancers. However, public health recommendations must balance these potential benefits with the risks, particularly the heightened risk of lung cancer associated with coffee intake. Future research should focus on elucidating dose–response relationships, exploring causal mechanisms, and conducting detailed analyses across diverse population subgroups. Such efforts will help refine dietary guidelines, ensuring they are tailored to maximize health benefits while minimizing potential risks.

Author contribution Setor K. Kunutsor: conceptualization, methodology, data curation, formal analysis, investigation, original draft, writing—review and editing. Andrea Lehoczki: methodology, investigation, writing—review and editing. Jari A. Laukkanen: data curation, investigation, writing—review and editing.

Data availability This is a narrative review; no new scientific data was generated, and all data are within the paper.

Declarations

Conflict of interest The authors declare no competing interests.

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