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Coffee vs. cancer: A comprehensive review of bioactive compounds, mechanisms, and epidemiological evidence

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Abstract
The health effects of coffee consumption remain a topic of ongoing debate. Earlier studies often linked coffee intake with negative health outcomes; however, recent research indicates that coffee consumption may not be harmful and may even provide protective health benefits. Several contemporary studies suggest an inverse association between coffee intake and the risk of developing certain cancers. While coffee consumption is not associated with an increased risk of most cancers, evidence regarding bladder and lung cancer remains inconsistent. In contrast, coffee intake appears to exert a protective effect against colorectal, liver, and breast cancers, particularly hepatocellular carcinoma and breast cancer among postmenopausal women. Coffee contains a wide range of bioactive compounds that may contribute to its health effects. Protective properties are largely attributed to polyphenolic antioxidants, anti-inflammatory components, and caffeine-related diterpenes such as cafestol, kahweol, and chlorogenic acids, which help reduce oxidative stress and inflammation. However, coffee also contains acrylamide, a potentially carcinogenic compound formed during roasting, especially when consumed in high amounts. The overall impact of coffee on cancer risk is influenced by multiple factors, including consumption level, metabolic rate, genetic variability, and individual lifestyle differences. Overall, current evidence supports a protective association between coffee consumption and liver cancer, with modest benefits observed for breast cancer, while associations with cancers of the oesophagus, pancreas, colon, kidney, bladder, ovary, and prostate remain conflicting and inconclusive.

Keywords: Coffee consumption, cancer risk, bioactive compounds, polyphenols, caffeine, cafestol

1. Introduction

Over the last century, coffee consumption has risen sharply, ranking it as the world's second most traded commodity behind petroleum (Wierzejska, 2015) [14]. Beyond its function as a stimulating beverage, coffee has become a focal point of substantial scientific inquiry due to its complex chemical composition and potential health effects (Ismail *et al*., 2021) [4]. Intensive research has been conducted on the connection between coffee consumption and cancer risk; however, results remain inconsistent across various types of cancer and different population groups (Nigra *et al*., 2021) [8]. Initial research on the spread of diseases has suggested a potential link between coffee consumption and an increased risk of bladder and pancreatic cancer (Snowdon & Phillips, 1984) [12]. Subsequent research utilising more advanced study designs and statistical techniques has largely alleviated public health concerns, as key organisations have concluded that coffee is not a carcinogen (Pauwels & Volterrani, 2021) [9]. Epidemiological studies have demonstrated that drinking coffee may decrease the likelihood of cancer through its activation of antioxidant and detoxification pathways. Studies conducted by Arab (2010) [15] revealed that there is a reverse correlation between coffee consumption and different types of cancer, such as liver, endometrial, and colorectal cancer, which may be linked to coffee's ability to control inflammatory responses and protect cells from damage caused by oxidative stress. Following analyses of multiple studies, this claim received further support. Studies conducted by Wang *et al*. (2016) [16] found a significant connection between increased coffee intake and reduced risks of liver, endometrial, prostate, and colorectal cancers. Studies by Yu *et al*. (2011) [24] likewise

Discovered a protective impact for the overall risk, notably in instances of liver and breast cancers. Recent studies have redirected their attention towards uncovering the potential anticancer properties of coffee and its bioactive compounds (Ismail *et al*., 2021) [4]. Research in the field of epidemiology shows a complex connection between coffee consumption and the occurrence of cancer (Tran *et al*., 2019) [13]. Certain cancer types have been found to have consistent inverse correlations with the amount of coffee consumed, whereas others exhibit positive correlations or no significant connections (Schmit *et al*., 2016) [11]. Research has shown that studies of mechanisms have clarified several routes by which coffee's components could alter the risk of cancer, such as modifying oxidative stress, repairing DNA damage, regulating cell cycles, and influencing apoptosis pathways (Bułdak *et al*., 2018) [1]. Interpreting epidemiological observations and creating evidence-based dietary guidelines relies heavily on grasping these mechanisms. This review synthesizes current scientific understanding of coffee's composition, its bioactive compounds, how they operate in cancer prevention, and the evidence connecting coffee intake to certain cancer types. The analysis centers on six types of cancer - renal, stomach, colorectal, breast, bladder, and gastric - which are informed by recent systematic reviews, meta-analyses, and mechanistic investigations (Deng *et al*., 2022; Li *et al*., 2022; Martimianaki *et al*., 2022; Rhee *et al*., 2022; Ellingjord-Dale *et al*., 2021) [2, 6, 7, 10, 3].

2. Background

The beverage coffee is a chemically complex substance comprising more than 800 volatile compounds. The composition varies substantially depending on the production and preparation techniques used. The chemical makeup of coffee beans is shaped by several variables, including the coffee species, cultivar, environmental factors during growth, and subsequent processing methods like roasting and grinding (Ismail *et al*., 2021) [4]. Roasting coffee causes substantial changes to its chemical makeup, converting the natural substances found in green beans into compounds resulting from the Maillard reaction. Throughout this process, the original components of green coffee undergo modification, while new compounds either form or accumulate in greater concentrations within the roasted (black) coffee beans (Bułdak *et al*., 2018) [1]. The primary processes involved in this established roasting phenomenon include the caramelization of carbohydrates and the breakdown of organic substances through pyrolysis (Nigra *et al*., 2021) [8]. This group comprises a wide range of chemical compounds with differing structures, physiological characteristics, and a molecular weight of between 200 and 1000 DA. These substances are also referred to as nutraceuticals, a term that reflects their presence in the human diet and their biological activity (Ismail *et al*., 2021) [4]. They comprise a wide variety of chemical compounds with distinct structures, physiological effects, and molecular weights ranging from 200 to 1000 DA. Studies have shown that green coffee beans are rich in bioactive compounds, but even though they are roasted and come into contact with hot water, dark coffee still contains and produces many new phytochemicals that are advantageous to consumers' well-being (Pauwels & Volterrani, 2021) [9].

3. Bioactive Compounds

Coffee is a chemically complex beverage containing hundreds of biologically active compounds that collectively contribute to its health effects, including potential cancer chemopreventive properties. The bioactivity of coffee is not attributable to a single compound but rather to the synergistic action of multiple constituents, including polyphenols, alkaloids, diterpenes, and Maillard reaction products formed during roasting (Ismail *et al*., 2021; Gaascht *et al*., 2015) [4, 23].

The main components of coffee can be grouped into several categories.

3.1 Alkaloids

In coffee, caffeine is the most common alkaloid, making up 1-2% of the dry weight in Arabica beans and up to 3% in Robusta beans. Caffeine is quickly absorbed within the gastrointestinal tract and easily passes through the blood-brain barrier. Other alkaloids present include theophylline and theobromine, which are found in lower concentrations than caffeine (Bułdak *et al*., 2018) [1].

3.2 Polyphenolic Compounds

Among coffee's bioactive constituents, chlorogenic acids (CGAs) are the predominant polyphenols, particularly abundant in green and lightly roasted coffee. The types of CGAs, including caffeoylquinic, feruloylquinic, and dicaffeoylquinic acids, exhibit potent antioxidant and anti-inflammatory properties (Esquivel & Jimenez, 2012; Wierzejska, 2015) [20, 14].

Studies have demonstrated that CGAs can lower oxidative DNA damage, adjust the activity of phase I and phase II detoxification enzymes, and impact cell signalling pathways associated with cancer development (Ismail *et al*., 2021; Bøhn *et al*., 2014) [4, 29]. Research experiments show that CGAs can slow down the growth of colorectal cancer cells and cause them to die, indicating a direct role in preventing tumor growth (Bułdak *et al*., 2018) [1]. Furthermore, CGAs may affect the balance of gut bacteria and reduce inflammation in the intestines, which are factors that contribute to colorectal cancer prevention (Bułdak *et al*., 2018; Schmit *et al*., 2016) [1, 11].

3.3 Deterpines

Cafestol and kahweol are primarily present in unfiltered coffee types such as French press and boiled coffee, which are lipid-soluble diterpenes. The compounds exhibit substantial biological activity, including the regulation of detoxification enzymes and anti-inflammatory properties (Ismail *et al*., 2021; Bøhn *et al*., 2014) [4, 29].

Experimental studies have found that cafestol and kahweol can induce apoptosis, suppress angiogenesis, and prevent tumor cell invasion by regulating pathways associated with carcinogenesis (Gaascht *et al*., 2015) [23]. Their particular importance in preventing cancer via chemotherapy has been especially highlighted in studies of colorectal and liver cancer (Nigra *et al*., 2021; Bułdak *et al*., 2018) [8, 1]. The brewing method has a considerable influence on the presence of these diterpenes, which may partly explain the heterogeneity in epidemiological research findings across different populations (Pauwels & Volterrani, 2021; Tran *et al*., 2019) [9, 13].

3.4 Melanoids and Browning Products
Maillard reactions take place between amino acids and reducing sugars during coffee roasting, resulting in melanoid formation. These compounds are responsible for the color, aroma, and flavour profile of coffee. Melanoids show significant antioxidant properties, displaying an *in vitro* antioxidant capacity of 725-750 μmol Trolox equivalent per gram, a value that can be tripled by incorporating sugar during the roasting process (Bułdak *et al*., 2018) [1].

4. Health Impacts of Key Compounds
4.1 Chlorogenic Acid
Chlorogenic acids possess significant antioxidant capabilities, enabling them to eliminate reactive oxygen species and diminish oxidative DNA damage, a crucial initial stage in carcinogenesis (Nigra *et al*., 2021; Bøhn *et al*., 2014) [8, 29]. Furthermore, CGAs exhibit anti-inflammatory properties, impacting pathways such as cyclooxygenase activity and inflammatory cytokine production (Ismail *et al*., 2021) [4].
Cancer models of the colon and rectum have demonstrated that CGAs possess the ability to restrict cancer cell proliferation, induce cell apoptosis, and enhance DNA repair mechanisms. Research carried out in living organisms as well as in laboratory conditions demonstrates that CGAs contribute substantially to the protective effects of coffee in preventing the onset of colorectal tumors (Bułdak *et al*., 2018) [1]. These effects are mediated by regulating oxidative stress, mitochondrial dysfunction, and cell cycle checkpoints.
CGAs boost the activity of phase I and phase II detoxification enzymes, leading to an increase in carcinogen removal and a decrease in their bioactivation (Gaascht *et al*., 2015; Bøhn *et al*., 2014) [23, 29]. A partial breakdown by gut bacteria may also have a positive effect on intestinal health and lower the risk of colorectal cancer (Schmit *et al*., 2016) [11].

4.2 Caffeine
Caffeine, the most thoroughly researched alkaloid in coffee, performs a dual function in the beverage, enhancing both its stimulating characteristics and biological repercussions. Caffeine also exhibits antioxidant and anti-inflammatory properties, stimulates the central nervous system and influences cell cycle regulation and DNA damage response pathways (Ismail *et al*., 2021; Wachamo, 2017) [4, 18].
Research into mechanisms indicates that caffeine can trigger apoptosis, inhibit the growth of cancer cells, and disrupt pathways associated with tumour development, notably in liver and colorectal cancer models (Bułdak *et al*., 2018; Gaascht *et al*., 2015) [1, 23]. Mendelian randomization studies suggest a possible association between caffeine consumption and a reduced risk of certain cancers, notably renal cell carcinoma and bladder cancer, a connection that aligns with a biological mechanism extending beyond the influence of lifestyle factors (Deng *et al*., 2022; Li *et al*., 2022) [2].
Caffeine's effects are complex and directly linked to the amount consumed. Frequent consumption of regular coffee can lead to physical adaptation, which may alter the impact of caffeine on the body, as noted by Lesar *et al*. (2025). Evidence from epidemiological studies also does not imply that a higher risk of breast cancer is associated with caffeine or coffee consumption (Ellingjord-Dale *et al*., 2021) [3].

4.3 Trigonelline
Trigonelline, a pyridine alkaloid found in coffee, participates in antioxidant activity and has been shown to affect oxidative stress pathways. Roasting triggers the breakdown of trigonelline into bioactive compounds such as nicotinic acid (niacin), possibly increasing coffee's health benefits (Ismail *et al*., 2021; Esquivel & Jimenez, 2012) [4, 20].
Caffeine and CGAs have been studied in greater detail, but studies have found that trigonelline has anti-cancer properties, including inhibiting the growth and spread of cancer cells in lab experiments, and may impact cellular redox balance and gene expression (Ismail *et al*., 2021; Gaascht *et al*., 2015) [4, 23].

4.4 Melanoids
The roasting of coffee beans leads to the formation of melanoidins, which being high-molecular-weight compounds that arise through Maillard reactions. Coffee's color, flavor, and antioxidant properties are attributed to these compounds (Wierzejska, 2015; Esquivel & Jimenez, 2012) [14, 20].
Melanoidins have metal-chelating, free radical-scavenging, and antimicrobial properties, and they could offer protective advantages in the gastrointestinal tract (Ismail *et al*., 2021) [4]. Undigested resistance allows them to reach the colon, thus impacting gut microbiota and inflammatory processes linked to colorectal cancer development (Bułdak *et al*., 2018; Bøhn *et al*., 2014) [1, 29].

4.5 Diterpenes
Coffee contains two primary diterpenes, namely cafestol and kahweol. These compounds are responsible for the lipophilic antioxidant properties of coffee and have been studied for their potential anticarcinogenic effects. The bioavailability of coffee is greatly affected by the method of preparation, with paper filtration typically removing diterpenes and resulting in unfiltered preparations containing significantly higher levels of these compounds (Bułdak *et al*., 2018) [1].

5. Molecular Mechanisms of Anticarcinogenic Action
The anticarcinogenic properties of coffee are attributed to the synergistic effect of multiple bioactive compounds, including caffeine, chlorogenic acids, diterpenes, trigonelline, and melanoidins. These compounds interact with multiple molecular targets involved in cancer development, their effects being dependent on the type of cell and the specific biological pathway. Coffee achieves its chemopreventive effects through multiple pathways, which involve oxidative stress, inflammation, detoxification, cell cycle regulation, apoptosis, and immune system modulation (Ismail *et al*., 2021; Gaascht *et al*., 2015) [4, 23].

5.1 Modulation of Oxidative Stress and Redox Homeostasis
Oxidative stress contributes to cancer initiation through key mechanisms including DNA damage, lipid peroxidation, and protein modification. Coffee polyphenols, specifically chlorogenic acids, are capable of efficiently removing free radicals, reducing intracellular ROS, and protecting genomic

integrity in normal cells (Nigra *et al*., 2021; Bøhn *et al*., 2014) [8, 29].

At a molecular level, the components in coffee activate the Nrf2 (nuclear factor erythroid 2-related factor 2) signalling pathway, leading to an increase in antioxidant and cytoprotective enzymes such as glutathione S-transferases, NAD(P)H quinone oxidoreductase-1, and heme oxygenase-1 (Ismail *et al*., 2021; Gaascht *et al*., 2015) [4, 23]. The enhanced antioxidant defense reduces the amount of oxidative DNA damage, which is a vital first step in the formation of cancer.

Research indicates that in cancer cells, coffee's active compounds can have an oxidising effect, elevating ROS levels above the threshold that cancer cells can endure, resulting in cell death (Ismail *et al*., 2021; Bułdak *et al*., 2018) [4, 1]. The potential of coffee to prevent cancer is also influenced by its dual electron transfer process.

5.2 Regulation of Phase I and Phase Ii Detoxification Enzymes

Research has shown that drinking coffee can affect enzymes responsible for the breakdown of foreign substances, ultimately reducing exposure to carcinogenic compounds present in food and the environment. Compounds like chlorogenic acids, cafestol, and kahweol, which have bioactive properties, inhibit the activation of phase I enzymes that form carcinogens by boosting phase II detoxification enzymes that facilitate the removal of carcinogens (Gaascht *et al*., 2015; Bøhn *et al*., 2014) [23, 29].

Decreasing the formation of DNA-reactive metabolites via detoxification leads to a reduction in mutations, thereby lowering cancer risk. These mechanisms are particularly relevant in digestive tract cancers where there is a high exposure to carcinogens from food (Tran *et al*., 2019; Poole *et al*., 2017) [13, 19].

5.3 Anti-Inflammatory Pathways

Chronic inflammation is generally considered a hallmark of cancer, contributing to the development, advancement, and growth of tumors. Coffee contains bioactive compounds that inhibit inflammatory pathways by halting COX-2 activity, reducing pro-inflammatory cytokine production, and modulating NF-κB signaling (Ismail *et al*., 2021; Wachamo, 2017) [4, 18].

Studies have found a connection between consuming coffee and decreased levels of inflammatory chemicals in the bloodstream, implying a broad anti-inflammatory impact (Loftfield *et al*., 2015) [21]. Cancer prevention is thought to be facilitated by coffee due to its ability to limit cell growth caused by inflammation and genetic damage within multiple types of tissue (Nigra *et al*., 2021; Pauwels & Volterrani, 2021) [8, 9].

5.4 Induction of Apoptosis and Cell Cycle Arrest

One of the most commonly reported anti-cancer mechanisms of coffee is its ability to induce programmed cell death and inhibit excessive cell proliferation. Experimental research has shown that coffee extracts and certain compounds such as caffeine, chlorogenic acids, cafestol, and kahweol can activate both intrinsic and extrinsic apoptosis pathways in cancer cells (Bułdak *et al*., 2018; Gaascht *et al*., 2015) [1, 23].

These outcomes comprise

- Activation of the caspase initiation pathways.
- Loss of mitochondrial membrane potential.
- Regulation of proteins that promote apoptosis and inhibit apoptosis.

Coffee components induce cell cycle arrest at the G0/G1 or G2/M phases by controlling cyclins and cyclin-dependent kinases, thus inhibiting the growth of cancer cells (Ismail *et al*., 2021; Bøhn *et al*., 2014) [4, 29].

5.5 Dna damage response and repair enhancement

DNA damage accumulation is a fundamental driver of carcinogenesis. Coffee polyphenols enhance DNA recognition and repair mechanisms, resulting in a decrease in mutation and chromosomal instability in normal cells (Ismail *et al*., 2021; Nigra *et al*., 2021) [4, 8].

At the same time, increased oxidative stress within cancer cells may exceed their repair capabilities, leading to apoptosis. The differential regulation of DNA repair pathways is believed to be the reason why coffee can harm cancerous cells while leaving healthy cells unharmed (Bułdak *et al*., 2018; Gaascht *et al*., 2015) [1, 23].

5.6 Modulation of Oncogenic Signaling and Gene Expression

Bioactive compounds in coffee influence gene expression and the pathways causing cancer that contribute to tumor growth and longevity. Studies indicate that the expression of oncogenes like c-Myc is inhibited, and the regulation of transcription factors involved in proliferation, angiogenesis, and metastasis is also affected (Ismail *et al*., 2021; Gaascht *et al*., 2015) [4, 23].

Research has discovered that coffee can affect microRNAs and zinc finger transcription factors, potentially aiding in the prevention of cancer cells from spreading and invading, thereby slowing down tumor growth (Ismail *et al*., 2021) [4].

5.7 Immune Modulation

Studies suggest that consuming coffee influences the immune system by controlling cytokine production and the functioning of immune cells. Reducing systemic inflammation and improving immune system tracking may indirectly help prevent cancer (Loftfield *et al*., 2015; Arab, 2010) [21, 15]. The compound's ability to modulate the immune system may be particularly important in cancer cases associated with prolonged inflammation and an imbalance of the immune system (Nigra *et al*., 2021) [8].

6. Renal Cancer and Coffee

Kidney cancer, specifically renal cell carcinoma (RCC), is the most common type of cancer in the kidneys and accounts for approximately 3% of all cancers. The causes of RCC are complex and involve multiple factors, which have been identified as including high blood pressure, being overweight, smoking, and a family history. Investigations have been conducted into coffee consumption as a potential modifiable risk factor (Rhee *et al*., 2022) [10].

6.1 Epidemiological Evidence

Epidemiological research consistently indicates a potential protective relationship between drinking coffee and the risk of renal cancer. A 2022 meta-analysis of cohort studies by Rhee *et al*. (2022) [10] discovered a reverse correlation between coffee consumption and the incidence of renal cell carcinoma, where greater intake was associated with a lower risk. A study by Li *et al*. (2022) [6] used Mendelian randomization to discover that genetically predicted coffee and caffeine consumption were associated with a decreased risk of renal cell carcinoma, which helped to control for confounding factors and reverse causation. These findings are consistent with broader umbrella and narrative reviews, which indicate a beneficial risk profile for coffee concerning kidney-related cancers (Nigra *et al*., 2021; Poole *et al*., 2017) [8, 19].

6.2 Proposed Mechanisms

Mechanisms that could protect against renal cell carcinoma involve coffee's ability to lower oxidative stress through polyphenolic antioxidants, regulate inflammatory pathways associated with kidney cancer, and enhance liver detoxification. Oxidative stress can severely impact the kidney in multiple disease states, and coffee's antioxidants may potentially stop the formation of RCC by safeguarding renal epithelial cells from DNA-damaging oxidative damage (Rhee *et al*., 2022) [10].

7. Stomach Cancer and Coffee

Gastric cancer is a significant global health issue, representing the fifth most frequent cancer worldwide and the third biggest contributor to cancer-related deaths. Gastric cancer development is influenced by a variety of environmental and genetic factors, with the H. pylori infection being the most well-documented risk factor to date (Martimianaki *et al*., 2022) [7].

7.1 Epidemiological Evidence

Epidemiological evidence from stomach cancer indicates that it is a heterogeneous and inconsistent condition. A pooled analysis of Martimianaki *et al*. (2022) [7] as part of the StoP Project found no significant protective effect overall, but variations were observed between sex, geographic area, and consumption levels. Tran *et al*. (2019) [13] conducted a large prospective cohort study, which showed a mix of results that differed according to the type of coffee consumed and the specific subtype of digestive cancer. Earlier investigations into the risk of gastric cancer have been influenced by potential confounding variables, such as smoking and brief follow-up periods, as observed in prior studies (Pauwels & Volterrani, 2021; Wierzejska, 2015) [9, 14]. Epidemiological data currently suggest that there is no evident correlation between these variables and the risk of developing stomach cancer.

7.2 Proposed Mechanism

Coffee's potential protective mechanisms against gastric cancer involve antimicrobial effects against *H. pylori* and other disease-causing microorganisms, antioxidant protection for gastric epithelial cells, and regulation of gastric acid release. On the other hand, suggested factors contributing to increased risk include stimulation of gastric acid release, which could potentially harm the gastric lining, and exceptionally high consumption, which may compromise the integrity of the gastric mucosa (Martimianaki *et al*., 2022; Pauwels & Volterrani, 2021) [7, 9].

8. Colorectal Cancer and Coffee

Globally, colorectal cancer ranks as one of the most prevalent malignancies, with incidence and mortality rates exhibiting marked geographical disparities. Factors in the environment, such as components of the diet, play significant roles in the development of colorectal cancer (Schmit *et al*., 2016) [11].

8.1 Epidemiological Evidence

Evidence from epidemiological studies suggests a protective association between coffee consumption and colorectal cancer, a type of digestive cancer. A large prospective cohort study led by Schmit *et al*. (2016) [11] discovered an inverse correlation between coffee consumption and the risk of colorectal cancer. Additional evidence comes from meta-analyses of cohort studies, which reveal a lower incidence of colorectal cancer in individuals who consume a considerable amount of coffee (Wang *et al*., 2016; Yu *et al*., 2011) [16, 24]. Results from reviews of umbrella studies, which include multiple meta-analyses, confirm that coffee consumption is associated with a lower risk of colorectal cancer, particularly colon cancer (Zhao *et al*., 2020; Poole *et al*., 2017) [22, 19]. Consistent results from diverse study designs strengthen the evidence in epidemiology.

8.2 Proposed Mechanism

Several mechanisms are probably responsible for coffee's protective impact on colorectal cancer. The direct cytotoxic effects on cancer cells through the generation of reactive oxygen species and the induction of apoptosis represent one crucial pathway. Furthermore, coffee may positively affect the composition of gut microbiota due to its antimicrobial properties, which in turn have implications for intestinal barrier function, immune system regulation, and the reduced translocation of bacterial lipopolysaccharides (endotoxins) that could lead to chronic inflammation and cancer development (Bułdak *et al*., 2018) [1].

The combination of antioxidant effects that protect normal colorectal epithelial cells from damage caused by oxidative insults and enhanced detoxification of carcinogenic substances (such as heterocyclic amines and polycyclic aromatic hydrocarbons in grilled or charred foods) likely plays a role in preventing cancer. Additionally, the prebiotic-like characteristics of coffee polyphenols, specifically their partial breakdown by colonic bacteria during fermentation, may yield short-chain fatty acids (particularly butyrate), which have a protective impact on colonocyte differentiation and barrier function (Bułdak *et al*., 2018) [1].

9. Breast Cancer and Coffee

Globally, breast cancer is the most prevalent cancer in women and the second most common cause of cancer-related deaths in females. Established risk factors include reproductive factors, hormone replacement therapy, alcohol consumption, obesity, and physical inactivity.

9.1 Epidemiological Evidence

Epidemiological research generally indicates that there is insufficient proof to show a correlation between coffee consumption and an elevated risk of breast cancer. A study published by Ellingjord-Dale *et al*. (2021) [3] found no causal relationship between genetically predicted coffee consumption and breast cancer, suggesting that previous reported associations in observational studies could be due to confounding factors. Epidemiological evidence supports the safety of coffee consumption in relation to breast cancer, with umbrella reviews and meta-analyses also reaching similar conclusions. These analyses found no increased risk of breast cancer from coffee consumption and, in certain groups, a potential weak inverse association, although this is not consistently observed (Alicandro *et al*., 2017; Poole *et al*., 2017) [17, 19].

9.2 Proposed Mechanism

In some experimental systems, coffee's polyphenolic components have been found to have estrogenic properties; however, the evidence from Mendelian randomization does not support the idea that coffee consumption is a concern for the development of breast cancer. The complexities of estrogen signaling in breast tissue, the various pathways through which coffee polyphenols may impact cancer development, and the potential benefits of antioxidant and anti-inflammatory components may counterbalance any theoretical estrogenic concerns (Ellingjord-Dale *et al*., 2021) [3].

10. Bladder Cancer and Coffee

Bladder cancer, one of the most prevalent forms of urologic malignancies, is notably associated with the most established risk factor being tobacco smoking. Research on coffee consumption has been inconclusive regarding its potential link to bladder cancer.

10.1 Epidemiological Evidence

Research in epidemiology has discovered a continually expanding body of evidence indicating a neutral to protective relationship between coffee consumption and the risk of bladder cancer. Research conducted by Deng *et al*. (2022) [2] discovered a protective association between genetically predicted coffee consumption and bladder cancer, countering earlier observational studies that suggested a possible increased risk. Studies of modern research indicate that previous positive associations may have been misrepresented due to smoking, a major bladder cancer risk factor that is strongly associated with coffee consumption (Nigra *et al*., 2021; Arab, 2010) [8, 15]. Recent umbrella reviews have discovered that coffee consumption is not associated with an elevated risk of bladder cancer and could potentially provide some protection, as indicated by Poole *et al*. (2017 and Zhao *et al*. (2020) [19, 22].

10.2 Historical Context and Current Understanding

Initial studies on the spread of disease found evidence suggesting a possible higher risk of bladder cancer associated with coffee consumption. Follow-up research featuring more sophisticated study designs and statistical techniques has not consistently verified these correlations. The Mendelian randomization findings yield robust evidence against a harmful link, suggesting possible protective advantages. The protective mechanisms may include antioxidant and anti-inflammatory effects reducing oxidative damage to the bladder urothelium, potential antimicrobial effects reducing chronic urinary tract infections, and direct antiproliferative effects on bladder cancer cells (Deng *et al*., 2022) [2].

11. Gastric Cancer and Coffee

Gastric cancer constitutes a considerable global health burden, especially in East Asian nations with a high incidence rate. Risk factors known to increase the likelihood of a condition include H. pylori infection, smoking, high salt intake, and specific genetic variations (Martimianaki *et al*., 2022; Pauwels & Volterrani, 2021) [7, 9].

11.1 Epidemiological Evidence and Analysis

Epidemiological studies have investigated the association between coffee consumption and the risk of gastric cancer. The available data is varied, with certain studies indicating a heightened risk at extremely high levels of consumption, whereas others document preventive relationships or inconclusive results (Martimianaki *et al*., 2022; Pauwels & Volterrani, 2021) [7, 9].

Differences in study populations, methodologies for evaluating coffee consumption, cancer classification and diagnosis techniques, and controls for confounding factors may underlie the variation in findings. Reverse causation, such as individuals developing early gastric cancer precursor lesions cutting back on coffee consumption because of gastrointestinal symptoms, may influence estimates to appear as if there is a heightened risk (Martimianaki *et al*., 2022) [7].

11.2 Mechanistic Considerations

Coffee consists of compounds with potential health benefits (polyphenolic antioxidants, antimicrobial agents) and compounds which may influence stomach function (caffeine and related alkaloids that stimulate gastric acid release). The net outcome is probably influenced by the level of consumption, personal vulnerability, the presence of a concurrent *H. pylori* infection, and genetic variations that impact caffeine metabolism (Martimianaki *et al*., 2022; Pauwels & Volterrani, 2021) [7, 9].

12. Comprehensive Cancer Perspectives

Researchers led by Nigra *et al*. (2021) [8] compiled a decade's worth of evidence on coffee's potential anticancer properties, analyzing various types of cancer. The review found that an extra 2 cups of caffeinated coffee were associated with a 27% drop in the risk of cancer, whereas decaffeinated coffee consumption was linked to a 14% decrease in risk (Nigra *et al*., 2021) [8]. This discovery suggests that both caffeine and non-caffeine compounds contribute to protective effects, with the extent of this contribution varying between caffeinated and decaffeinated products.

Poole *et al*. (2017) [19] analyzed multiple meta-analyses and found that coffee is consistently linked with lower overall mortality rates and lower incidence of several specific types of cancer, without any significant evidence of harm. Zhao *et al*. (2020) [22] found that coffee offers protection against liver, endometrial, and skin cancers, with no conclusive evidence of higher cancer risk for any major type of cancer. Alicandro *et al*. (2017) [17] also pointed out that coffee does not significantly increase cancer risk and may have positive effects on cancers linked to oxidative stress.

Scientific studies support these epidemiological findings, with coffee's polyphenols - such as chlorogenic acid - exhibiting potent free radical-scavenging properties, whereas caffeine shows antiproliferative and pro-apoptotic effects. According to Gaascht *et al*. (2015) [23], coffee can be considered a "natural multitarget pharmacopeia," affecting multiple cancer characteristics, including inflammation, DNA damage, angiogenesis, and cell proliferation (Gaascht *et al*., 2015) [23]. Esquivel and Jimenez (2012) [20] highlighted the functional characteristics of coffee components, noting their ability to regulate cellular metabolism and reduce oxidative stress crucial processes in cancer prevention. According to Loftfield *et al*. (2015) [21], drinking coffee is associated with positive inflammatory and immune markers, suggesting a biological explanation for its health benefits.

Pauwels and Volterrani (2021) [9] conducted a thorough evaluation of the relationship between coffee consumption and cancer risk based on the current understanding of the topic. Research has established a significant link between coffee consumption and a reduced cancer risk, a relationship primarily attributed to the presence of polyphenolic compounds and other antioxidants. The assessment drew attention to the complex relationship between coffee and cancer, with existing evidence varying according to the particular cancer type.

A review of coffee in cancer prevention was updated by Ismail *et al*. (2021) [4] combining evidence from various research methods. The review underscored the different ways in which coffee components exhibit anticarcinogenic properties, including antioxidant and anti-inflammatory actions, modification of phase I and II detoxification enzymes, induction of apoptosis and cell cycle arrest in cancer cells, and enhancement of DNA damage repair in normal cells.

Some cancer sites have undergone more intensified research. Salari-Moghaddam *et al*. (2019) [27] discovered no heightened risk for ovarian cancer and observed a primarily neutral outcome across various coffee types and caffeine levels. Researchers conducted a meta-analysis of various types of cancer and found that coffee consumption may have either neutral or protective effects, particularly in reducing the risk of liver and endometrial cancers (Kennedy & Abraham, 2017) [28]. Bøhn *et al*. (2014) [29] combined epidemiological and molecular evidence to conclude that coffee's components may prevent cancer development by affecting DNA repair, antioxidant defenses, and inflammation.

Long-term cohort studies also support the notion that coffee contributes to a reduced risk of cancer mortality. Tamakoshi *et al*. (2011) [25] discovered in the extensive Japanese JACC cohort that habitual coffee drinkers showed a decrease in overall cancer mortality, mainly resulting from liver disease. Park *et al*. (2017) [30] found similar results in the US across multiethnic groups, with coffee consumption linked to lower total and cause-specific mortality rates, encompassing cancer-related deaths. Several studies have proposed that coffee could alter the impact of specific environmental carcinogens. Porta *et al*. (2003) [26] stated that coffee may modify the effects of carcinogenic exposures through its impact on detoxification enzymes. Wachamo (2017) [18] equally characterised the dual nature of coffee's health impacts but concluded that, on balance, its benefits outweigh possible risks.

These findings collectively suggest that coffee is not a carcinogenic drink, and it may offer substantial protection against several major types of cancer, specifically liver, endometrial, colorectal, and possibly breast and prostate cancers. Evidence suggests that moderate coffee consumption has a generally beneficial impact on reducing cancer risk, although findings can differ depending on the population, the amount consumed, and the brewing method used.

Research has consistently demonstrated that coffee and its components have anticarcinogenic properties *in vitro* and in animal studies, but translating these results into human cancer prevention requires integrating epidemiological research, a mechanistic understanding, and consideration of dose-response relationships, individual susceptibility factors, and potential interactions with other dietary and lifestyle factors (Ismail *et al*., 2021; Nigra *et al*., 2021; Pauwels & Volterrani, 2021; Bułdak *et al*., 2018) [4, 8, 9, 1].

13. Summary

Scientific evidence indicates that coffee consumption is linked to a decreased risk of several cancer types, with the connection being multifaceted and varying across different forms of malignancy. Consistency in protective associations is most evident for liver, ovarian, thyroid, and endometrial cancers and melanoma, backed by robust mechanistic evidence from *in vitro* and animal studies (Nigra *et al*., 2021; Bułdak *et al*., 2018) [8, 1].

The available evidence indicates that the following cancer types are under examination in this review.

- Prospective cohort and Mendelian randomization studies indicate a protective link between coffee consumption and renal cancer, with a risk reduction that varies according to the amount consumed (Li *et al*., 2022; Rhee *et al*., 2022) [6, 10].
- Epidemiological studies provide consistent evidence, backed by *in vivo* and *in vitro* mechanistic data showing reduced tumor development and cancer cell growth inhibition, which supports the idea that coffee consumption has a protective effect (Bułdak *et al*., 2018; Schmit *et al*., 2016) [1, 11].
- Research suggests that there is no causal link between coffee consumption and an increased risk of breast cancer (Ellingjord-Dale *et al*., 2021) [3].
- Findings from Mendelian randomization suggest a protective link between coffee consumption and bladder cancer, which contradicts initial concerns about possible cancer-causing effects (Deng *et al*., 2022) [2].
- Evidence for gastric and stomach cancer remains inconsistent, with some research suggesting a higher risk at extremely high consumption levels in certain groups, yet other studies show either no or potentially beneficial effects. Variation in findings can be attributed to reverse causation and population-specific factors (Martimianaki *et al*., 2022; Pauwels & Volterrani, 2021) [7, 9].

Coffee's bioactive compounds, specifically chlorogenic acid, caffeine, trigonelline, melanoids, and diterpenes, have numerous biological effects that are associated with cancer prevention. These compounds activate normal cells' antioxidant and anti-inflammatory pathways, improve DNA repair capabilities, trigger cell cycle arrest and apoptosis in cancer cells, and modify metabolic pathways. It appears to be beneficial against many cancer types when consumed in moderate amounts, approximately 2-5 cups per day (Nigra *et al*., 2021; Bułdak *et al*., 2018) [8, 1].

Key considerations include population-specific variation in genetic susceptibility, differences in coffee preparation methods impacting bioactive compound composition, individual differences in caffeine metabolism, and the need to consider coffee consumption within the broader context of overall dietary and lifestyle patterns (Pauwels & Volterrani, 2021; Bułdak *et al*., 2018) [9, 1]. Although coffee has been found to be non-carcinogenic, and substantial research indicates it may have a protective effect against various cancer types, it should be regarded as part of a multifaceted strategy for preventing cancer that incorporates other proven measures, including regular exercise, sufficient consumption of fruits and vegetables, moderate alcohol intake, abstaining from tobacco, and maintaining a healthy body weight (Nigra *et al*., 2021; Bułdak *et al*., 2018) [8, 1].

14. Conclusion

Scientific research has intensively examined coffee consumption in relation to cancer risk and prevention. This beverage comprises a substantial quantity of bioactive compounds, including chlorogenic acid, which is the most prevalent polyphenol, caffeine, trigonelline, melanoids, and diterpenes. These compounds display properties as antioxidants, anti-inflammatories, and anticarcinogens via several biological pathways.

Epidemiological research indicates a protective link between coffee consumption and various types of cancer, including renal cancer, colorectal cancer, and bladder cancer. Gastric cancer evidence remains diverse, with certain populations displaying elevated risk at extremely high consumption levels. Mendelian randomization studies offer evidence that supports causal protective associations, thereby bolstering inferences that go beyond those based on conventional observational data. Studies have shown that the components in coffee consistently demonstrate a reduction in cancer cell proliferation, induce programmed cell death, enhance DNA repair mechanisms, and influence detoxification pathways.

A thorough analysis of the available data suggests that moderate coffee consumption (2-5 cups per day) is likely safe and potentially has health benefits in reducing the risk of cancer. Coffee's protective effects are thought to stem from the interaction of multiple bioactive compounds and how cells respond to oxidative and anti-inflammatory stress. More research is needed, but available data indicate that coffee consumption can be integrated into cancer prevention plans as one aspect of a multifaceted approach that includes other proven preventive measures.

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