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Review

COFFEE CONSUMPTION AND FEMALE CANCERS: A NARRATIVE REVIEW OF RECENT EVIDENCE

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ABSTRACT

Coffee contains a wide variety of bioactive compounds including polyphenols, melanoidins, and diterpenes. Coffee consumption may have either neutral or beneficial effects toward human health. In this review, we summarize current evidence regarding the association between coffee consumption and breast, endometrial and ovarian cancer, as well as molecular mechanisms underlying the beneficial effects of coffee. The epidemiological evidence suggests a protective effect of coffee towards postmenopausal breast and endometrial cancer. However, no statistical association was found between coffee and ovarian cancer. The chemo-preventive effects of coffee phytochemicals may include activation of anti-oxidative and anti-inflammatory response. Finally, coffee bioactive components where shown to inhibit cancer cell proliferation and metastasis, as well as modulation of impaired angiogenesis.

1. Introduction

The global burden of cancer affects about 15 million incident cancer cases, 8 million deaths, and almost 200 million disability-adjusted life years (DALYs) worldwide (1). Among the most diagnosed tumors in men, prostate, lung and colorectal cancers have the highest impact in terms of survival and quality of life (2, 3). Breast, endometrial and ovarian cancers are the most frequently diagnosed cancers and among the leading causes of cancer death among females (4, 5). In 2012, worldwide and European estimates of women diagnosed with breast cancer within the 5 years prior were over 6.2 million, while 1.8 million have been diagnosed with breast cancer during the last 5 years worldwide and in Europe, respectively (6). Estimates of the same year showed that over 1.2 million women worldwide were diagnosed with endometrial cancer in the last 5 years, accounting for about 400,000 in Europe (6). The impact of ovarian cancer is slightly lower, totaling 587,000 cases worldwide, 157,000 in Europe, respectively (6, 7, 8, 9). In 2013, the most common cause for DALYs in women was breast cancer (13.1 million), followed by endometrial cancer which caused 6.9 million DALYs with 85% occurring in developed countries. DALYs for ovarian cancer has increased since 1990 from 2.7 to over 4 million DALYs, making it the 12th contributor of death and disability among cancers worldwide (1). When compared to all causes of death, the percentage of cancer death has risen from 12% in 1990 to 15% in 2013. This accounts for deaths due to ovarian cancer which were about 158,000 worldwide in 2013 (10). Five-year survival of breast cancer rose to 85% or higher in 17 countries worldwide; estimates of 5-year survival from endometrial cancer have been reported to range from less than 50% to more than 70%; for women diagnosed with ovarian cancer in 2005-09, 5-year survival was 40% or higher only in Ecuador, the USA, and 17 countries in Asia and Europe (10). Significant improvements in early diagnosis and treatment have led to decreased mortality in the last two decades (11-15). However, evaluation of potential risk factors and improving preventive actions is needed in order to decrease the global burden of such a disease. Research over the last decades explored the potential association between dietary factors and human health, suggesting that diet may affect the risk of non-communicable disease (16, 17). Among others, coffee consumption has been the focus of major attention due to its widespread consumption among populations worldwide (18, 19). Results from meta-analyses showed that coffee intake was associated with lower mortality rates, including cancer mortality (20). This last piece of evidence is in line with

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an overall association between coffee consumption and risk of various cancers, including decreased risk of melanoma (21), liver (22), prostate (23), pancreatic (24), and colorectal cancers (25). The chemopreventive effects of coffee phytochemicals may include activation of anti-oxidative and anti-inflammatory response (26). Moreover, coffee bioactive components were shown to inhibit cancer cell proliferation and metastasis, as well as modulation of impaired angiogenesis (27). However, current evidence of the association between coffee consumption and female cancers remain in contrast. In this review we summarized current evidence regarding the association between coffee consumption and breast, endometrial and ovarian cancer, as well as molecular mechanisms underlying the beneficial effects of coffee.

2. Breast Cancer

The relation between coffee drinking and risk of breast cancer has been unclear for a long time. Previous meta-analyses showed borderline associations between coffee consumption and risk of breast cancer, despite the fact that most of the association was driven by case-control studies and that the analysis restricted to prospective cohort studies was not significant (28, 29). A more recent report focused the attention on prospective cohort studies (21 studies accounting for 1,068,098 participants and 36,597 breast cancer cases) for the sole purpose of drafting stronger evidence; confirming previous null results for the risk of breast cancer associated with the highest versus the lowest consumption of coffee (relative risk [RR] = 0.96, 95% confidence interval [CI]: 0.93-1.00) (30). However, the dose-response analysis showed an inverse relationship between increasing coffee consumption and breast cancer risk in post-menopausal women, with a 10% reduction in postmenopausal cancer risk associated with consumption of 4 cups of coffee per day (RR 0.90; 95% CI 0.82 to 0.99).

Besides menopausal status, further insights were conducted on hormonal and genetic aspects of breast cancer. Results from pooled data of case-control studies showed an inverse association between coffee consumption and likelihood of breast cancer in estrogen receptor negative women (28). Moreover, a significant association was also found between women diagnosed with breast cancer and BRCA1 mutations (29). Individual studies further investigated the association between coffee consumption and breast cancer risk in relation to specific polymorphisms. For instance, a study conducted on Swedish women reported that coffee consumption may affect estrogen receptor-positive breast cancers in women with the CYP1A2*1F AA (31) and C genetic polymorphism (32). However, results are not univocal and protection from breast cancer has been also observed in cases of high coffee consumption irrespective of the CYP1A2 genotype (33).

3. Endometrial Cancer

Studies on coffee consumption and endometrial cancer risk showed more consistent results over time, with about 10% decreased risk of endometrial cancer in women consuming 1 cup/d of coffee and a further decrease in risk estimated with higher amounts of coffee in a linear-dose manner (34-36). When considering multiple dietary factors, a study conducted in a large sample of European (from the European Prospective Investigation into Cancer and Nutrition [EPIC] study) and American women (from the Nurses' Health Studies [NHS/NHSII]) showed that only coffee was consistently associated with decreased risk of endometrial cancer in both cohorts, while 8 other dietary factors were found associated with endometrial cancer risk in the EPIC study (total fat, monounsaturated fat, carbohydrates, phosphorus, butter, yogurt, cheese, and potatoes) but not in the NHS/NHSII (37). A more recent meta-analysis of 12 prospective cohort studies including 1,404,541 participants and 10,548 endometrial cancer cases showed that increasing coffee consumption by 4 cups/d of coffee was associated with a 20% reduction in total endometrial cancer risk (RR = 0.80, 95% CI: 0.72-0.89) and 24% reduction in postmenopausal cancer risk (RR = 0.76, 95% CI: 0.69-0.83) (38). Moreover, additional analyses exploring the role of potential confounding factors and effect modifiers showed rather reinforcing evidence of the association between coffee and endometrial cancer risk - lower risk in a body mass index higher than 25 $kg/m^2$and in those who never used hormone therapy (36, 38).

4. Ovarian Cancer

Previous reports, especially from case-control studies, warned of a possible direct association between coffee intake and ovarian cancer, showing women who consume higher amounts of coffee in a dose-related manner show a higher likelihood of having cancer. Results from more recent cohorts did not confirm such association and a pooled analysis of 7 prospective cohort studies, including 3,236 cases of ovarian cancer, showed an insubstantial association of an increment of 1 cup/d of coffee (RR = 1.02, 95% CI: 0.99-1.05) (39). Overall, current evidence did not show any direct association between coffee consumption and ovarian cancer risk.

5. Antioxydant and anti-inflammatory actions

Previous Chemo-preventive effects of coffee are generally attributed to its high antioxidant activity (40). Coffee is a rich source of dietary antioxidants and its wide consumption worldwide makes it the major contributor to dietary antioxidant intake (41). Growing evidence suggests that the inverse relationship between dietary coffee intake and female cancer risk could be mediated by several molecular mechanisms; in particular i) by protection against oxidative stress and oxidative damage (ex. DNA damage), ii) by detoxification of carcinogens, iii) by inhibition of carcinogenesis via alteration of cell proliferation, cell cycle and induction of apoptosis (42-45). Coffee has been found to be one of the major contributors to antioxidants in diet (46). The antioxidant effects of coffee reported in experimental studies depend on the wide variety of bioactive compounds contained in coffee, including caffeine and trigonelline, diterpens, such as cafestol and kahweol, polyphenols, such as chlorogenic, ferulic, caffeic and n-coumaric acids, and finally melanoidins that are synthesized during the roasting process (47-49). Among the most studied compounds, polyphenols have demonstrated the strongest evidence from prospective cohort studies in decreasing mortality risk (50, 51) and, more specifically, affecting the risk of certain cancers (52-54). Data from in vitro and in vivo studies suggests that coffee and its components, being chemo-preventive agents, could interfere with different stages of the cancerous process i) by blocking the initiation

process of cancerogenesis and ii) by suppressing the promotion and progression of cancerogenesis. Blocking of the initiation process implicates scavenging reactive oxygen species (ROS), produced in both the physiological cell and in stressful conditions, detoxification of carcinogens, and by inducing the repair process of damaged DNA (55). On the other hand, suppression of promotion and progression of cancerogenesis includes inhibition of cell proliferation, induction of the cell's cycle arrest, and redirection of the cell to apoptosis (55). Coffee was shown to be one of the most potent inducer of nuclear factor (erythroid-derived 2)-like 2 (Nrf2) (56). Nrf2 is a transcription factor that binds to electrophile (ARE) response elements and regulates transcription of a range of defense enzymes, such as heme oxygenase-1 (HO-1), glutathione S-transferase (GST), and NAD(P)H:quinone oxidoreductase 1 (NQO1).

6. Sex hormone regulation

Coffee and caffeine intake have been associated with circulating levels of sex hormone-binding globulin (SHBG) in both, premenopausal and postmenopausal woman (57-61). SHBG is one of the carriers of estrogen and androgen. By binding to sex hormones, SHBG is inhibiting their function and influencing their bioavailability (62). High levels of circulating estrogens are known to be risk factors for breast, endometrial and ovarian cancer (63); and the inverse association between coffee and caffeine intake and estrogen levels has been reported (64, 65). However, a recent report demonstrated no association between decaffeinated coffee intake and plasma SHBG levels, suggesting that caffeine could be a key component of coffee accountable for the association with SHBG levels (66). Based on the results, the author hypothesized that another mechanism could account for the plausible effects of coffee. Coffee and its components modulate the expression and activity of liver enzymes (67). Since SHBG is primary synthesized and metabolized in the liver (68), coffee intake may regulate SHBG metabolism, which in turn can influence circulating levels of SHBG.

7. Coffee and metabolic health

High body weight and type-2 diabetes have been associated with an increased risk of several cancers (69, 70). Besides the action on systemic inflammation and sex steroids already discussed, these metabolic disorders may affect cancer risk through several other mechanisms involving insulin, insulin-like growth factor (IGF)-1, and adipokines(71). IGF-1 is produced in the liver under the stimulus of GH acting on the GH receptor (GHR). Both insulin and IGF-1 receptors are expressed in several tissues of the body and activate mitogenic pathways resulting in cell proliferation (72, 73). Besides insulin-related issues, other factors, such as circulating adipokines (including leptin and adiponectin) are also abnormal in obesity and type-2 diabetes and might affect cancer risk. In fact, leptin can enhance endothelial cell growth and suppress apoptosis through a BCL2-dependent mechanism (thus affecting risk of hormone-dependent neoplasms, such as female cancers), while adiponectin inhibits inflammation, atherogenesis, angiogenesis, and insulin resistance (72).Coffee has been suggested to exert beneficial effects toward metabolic health (74, 75); several studies have indeed reported an inverse association between coffee consumption and metabolic syndrome components, such as obesity, impaired glucose tolerance, dyslipidemia or hypertension(76-86). Coffee and caffeine intake have been shown to improve insulin sensitivity through stimulation of insulin-mediated uptake of glucose (87). Moreover, coffee has been associated with higher levels of circulating adiponectin and inversely associated with lepin levels, despite the fact that findings are not always consistent (88-93).

8. Limitation of studies on coffee and female cancers

The findings reported in current scientific literature on the relation between coffee consumption and female cancer risk should be considered in light of some limitations. The main issue refers to the potential confounding factors and effect modifier related to coffee drinking. Despite many of the studies included in the meta-analyses provided, such as additional data on smoking status, BMI status, and type of coffee (caffeinated or decaffeinated), separate datasets with risk estimates of such subgroups are not often available. Besides these variables, other residual confounding has not being investigated (i.e., education level and alcohol exposure). Moreover, no data on coffee brewing methods, preparation, and cup size are available. Finally, further information on metabolic (i.e., enzyme status), genetic (i.e., BRC1 and CYP1A2 genotypes), and histological aspects of cancer-subtypes are generally lacking in observational studies and do not allow an evaluation of different pathological pathways and the causal, exposure-disease relationship.

9. Conclusions

Public health implications should be briefly pointed out. As with regard to innovative genome-based prevention approaches of complex diseases (94-96).

Coffee consumption may have either neutral or beneficial effects toward female cancer risk. Current research provides robust evidence for this rediscovered association, however, additional efforts should be made in order to improve methodological design, data quality, and further information lacking in several studies (i.e., smoking status, type of coffee, etc.), in order to draft conclusions on the role that coffee drinking plays in such outcomes.

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