

Coffee and its Biologically Active Components: Is There a Connection to Breast, Endometrial, and Ovarian Cancer? – a Review

Anna M. Witkowska*, Iwona Mirończuk-Chodakowska, Katarzyna M. Terlikowska,
Kamila Kulesza, Małgorzata E. Zujko

Department of Food Biotechnology, Faculty of Health Sciences, Medical University of Białystok,
Szpitalna 37, 15–295 Białystok, Poland

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Coffee is an important dietary source of biologically active components, not to mention caffeine, phenolic acids, and diterpenes. It has been suggested that selected coffee secondary metabolites may beneficially modulate several mechanisms of anti-cancer protection. This literature review was intended to present current knowledge related to coffee and its components and hormone-dependent female cancers, such as breast, endometrial and ovarian cancer, and to identify gaps in research that may be exploited in the future. The search for studies was conducted through electronic databases. Publications on coffee composition, coffee preparation and brewing methods, *in vitro* and *in vivo* experiments with the use of substances naturally present in coffee, observational studies, and meta-analyses were collected. In population studies, the greatest attention has been paid to the anticancer effect of caffeinated coffee and/or caffeine. In general, most studies and meta-analyses indicated that there was no clear correlation between coffee and breast cancer or ovarian cancer. Some subgroups of women may benefit from coffee consumption. This is the case for post-menopausal women with regard to the risk of breast cancer and obese women with regard to the risk of endometrial cancer. This paper identifies a number of issues for future research, related to a better understanding of the anti-cancer mechanisms of coffee compounds and further research that would focus on specific target groups, taking into account both the different methods of coffee preparation and lifestyle factors that may influence the results.

INTRODUCTION

Coffee is one of the most popular beverages in the world because of its taste, aroma and stimulating properties, but the perception of coffee as a potentially health-promoting component of the diet is not very high in the global population [Samoggia & Riedel, 2019]. Except some cases, like pregnancy or sensitivity to some coffee compounds, coffee can offer many beneficial health effects [Grosso *et al.*, 2016, 2017a; Poole *et al.*, 2017; Wierzejska, 2016]. Interestingly, a recent exploratory study has shown that coffee consumption may modulate the expression of 297 genes in healthy women in different ways [Barnung *et al.*, 2018], thus affecting metabolic and inflammatory pathways. Several lines of evidence have linked coffee consumption to a reduced risk of cardiovascular diseases [Poole *et al.*, 2017; Rodríguez-Artalejo & López-García, 2018], cancer [Gapstur *et al.*, 2017; Grosso *et al.*, 2017a], neurodegenerative diseases [Liu *et al.*, 2016; Qi & Li, 2014], and diabetes [Ding *et al.*, 2014], as well as to a lower cancer mortality and all-cause mortality [Grosso *et al.*, 2017b; Gunter *et al.*, 2017; Poole *et al.*, 2017]. On a molecular basis, regular coffee consumption preserves the integ-

riety of DNA by decreasing spontaneous DNA strand breaks [Bakuradze *et al.*, 2015].

Cancers in women are a serious global health problem and a leading cause of death. They are responsible for a quarter of the deaths of women in Europe [European Commission, 2019] and a fifth in the USA [Centers for Disease Control and Prevention, 2019]. In sex hormone-dependent cancers, abnormal estrogen and progesterone levels are among the risk factors [Brown & Hankinson, 2015; Diep *et al.*, 2015]. With 24.2% incidence, breast cancer cases are the most common in women [Bray *et al.*, 2018]. In the global incidence of female cancers, endometrial (4.4%) and ovarian cancers (3.4%) rank sixth and eighth, respectively [Bray *et al.*, 2018].

Coffee is a source of biologically active compounds, many of which have anti-cancer properties. However, observational studies with humans, which focus mainly on coffee consumption (caffeinated or decaffeinated) and caffeine intake, show rather conflicting results for breast, uterine, and ovarian cancer. This literature review aims to present current research related to coffee and its components and hormone-dependent female cancers, such as breast, endometrial, and ovarian cancer, and to identify gaps in research that may be exploited in the future.

* Corresponding Author: Tel.: 85 6865090; Fax: 85 6865089
E-mail: anna.witkowska@umb.edu.pl

SEARCH STRATEGY

From the point of view of current knowledge, the search for studies from the last decade, *i.e.* from 2010 to 2019, was conducted through the electronic databases: Medline and Web of Science. Publications on coffee composition, coffee preparation and brewing methods, *in vitro* and *in vivo* experiments with the use of substances naturally present in coffee, observational studies, and meta-analyses were collected. In some cases, with the exception of case-control and epidemiological studies, studies that were important for this review, but outside the search period, were described as well. The search terms were multiple with “coffee” as a broad search term, and in combination with “breast cancer”, “ovarian cancer”, and “endometrial cancer” as the most critical for this review. The articles published in English that were relevant for this review were selected.

BIOACTIVE COMPOUNDS OF COFFEE

Roasted coffee beans are composed of several substances derived from different chemical groups, not to mention caffeine, phenolic acids, and diterpenes. Their contents in a coffee brew depend, to a large extent, on the type of coffee bean (*Coffea arabica* vs. *Coffea canephora* var. *robusta*), roasting parameters, as well as the methods of brewing. A coffee brew contains substances that are only specific to coffee, such as diterpenes – cafestol and kahweol [Gross

et al., 1997; Zhang *et al.*, 2012]. Others, such as caffeine, can be found in tea, cola-type beverages, and chocolate.

Caffeine

Caffeine is a heat-stable methylxanthine alkaloid (Figure 1) present mainly in coffee, tea, guarana, cola-type soft drinks, cacao, and chocolate. It is very soluble in boiling water. Depending on the type of coffee preparation (ground, instant) or brewing methods (boiling, filtering, French pressing), coffee may contain 19–803 mg caffeine per serving (Table 1). Decaffeinated coffee, in turn, presents considerably reduced caffeine content <9 mg/serving.

Several beneficial or adverse biological effects are attributable to caffeine. As an adenosine receptor antagonist, it is a central nervous system stimulant and anti-inflammatory agent [Madeira *et al.*, 2017]. *In vitro* studies have demonstrated cell cycle modulating and apoptotic properties of caffeine, mediated through various mechanisms, that can lead to tumor suppression [He *et al.*, 2003; Ito *et al.*, 2003; Saiki *et al.*, 2011]. Caffeine also exhibits antiproliferative activity in ovarian cancer cells, even several times higher than that of chlorogenic acid and caffeic acid [Tai *et al.*, 2010]. Besides, it may possibly alter circulating levels of luteal estrogens and sex hormone-binding globulin (SHBG), and thereby affect the development of cancers [Kotsopoulos *et al.*, 2009]. Variants in cytochrome P-450 (CYP) genes involved in caffeine metabolism may increase or decrease the risk of ovarian cancer development [Kotsopoulos *et al.*, 2009]. It has been

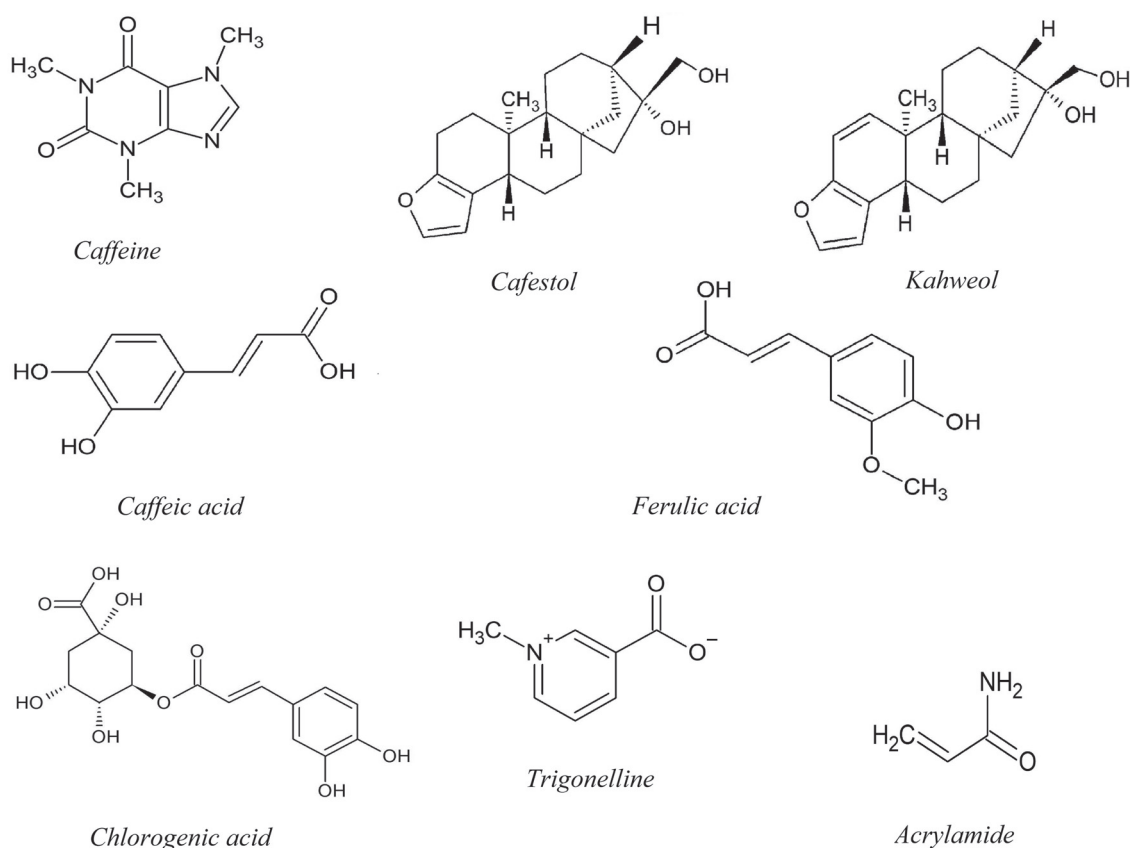


FIGURE 1. Chemical structure of major coffee compounds.

TABLE 1. Caffeine contents in varied coffee infusions*.

Coffee infusion type	Caffeine content (mg/L)	Caffeine content (mg per serving**)
Boiled/ Turkish	850–2330	201–552
Decaffeinated	1–37	0.24–8.77
Espresso	722–5334	19–144
Filtered	397–2008	81–416
French press	520–1564	123–371
Instant	390–2690	92–638
Mocha	924–2268	327–803

*adopted from: [dePaula & Farah, 2019]; **serving size for coffee: boiled/ Turkish, French press, instant, decaffeinated, 237 mL; espresso 27 mL; filtered 207 mL; mocha 354 mL.

suggested that caffeine from coffee may protect against endometrial cancer [Hashibe et al., 2015].

Coffee diterpenes

Diterpenes are organic compounds that consist of four isoprene units. In coffee, their main representatives include cafestol and kahweol (Figure 1), which are specific to the lipid fraction of coffee. In filtered coffees, this lipid fraction is absorbed by the cellulose paper filter [Gross et al., 1997]. Therefore, the contents of cafestol and kahweol in filtered coffee are negligible. Higher levels of diterpenes have been found in *Coffea arabica* than in *C. robusta* [Mensink et al., 1995]. The content of coffee diterpenes varies between 0.02–9 mg cafestol per serving and 0.02–7.2 mg kahweol per serving, depending on the coffee preparation procedure (Table 2).

Coffee diterpenes cause controversy because they may increase the levels of serum total cholesterol and LDL cholesterol fraction [Mensink et al., 1995]. Cafestol and kahweol demonstrate several biologically beneficial properties and are known as inducers of glutathione *S*-transferase, the enzyme which catalyzes detoxication reaction *via* conjugation of xenobiotics with the sulfhydryl group of glutathi-

one [Huber & Parzefall, 2005]. Consequently, conjugates are eliminated. Several lines of evidence connect coffee-specific diterpenes with anticancer properties. In male F344 rats, kahweol and cafestol (1:1) or only cafestol caused an increase in the level of hepatic O(6)-methylguanine-DNA methyltransferase (MGMT), an enzyme which is involved in the reversal of precarcinogenic damage of O(6)-alkylguanine, a DNA adduct formed by alkylating agents in a dose-dependent manner [Huber et al., 2003]. Anticarcinogenic activity of coffee diterpenes was observed in several cancer cell lines. Most of the papers on female cancers in conjunction with coffee diterpenes have so far been limited to mammary tumors. Antitumor activity of kahweol was tested in a few cancer cell lines. It has been shown to be manifested in both inhibited tumor cell growth and clonogenicity, and a decreased survival of cancer cells [Cárdenas et al., 2014]. These effects were mostly pronounced in estrogen-negative human breast cancer cells MDA-MB231, and were accompanied by the activation of caspases 3/7 and 9, and the release of cytochrome *c*. Kahweol increased the production of reactive oxygen species (ROS) and their cytotoxicity against breast cancer cells, but it did not affect the healthy cells [Cárdenas et al., 2014]. Other anticancer properties of kahweol are associated with its anti-angiogenic and anti-inflammatory characteristics [Cárdenas et al., 2011].

Cafestol has recently been hypothesized as a preventive compound in the pathology of diabetes [Mellbye et al., 2015]. In recent years, the link between diabetes and cancer has become of particular interest. With regard to the results of the research published in the last few years, diabetes can be thought of as a risk factor for certain types of cancer, including endometrial cancer. In an *in vitro* study, cafestol acutely stimulated insulin secretion from β -cells and improved insulin sensitivity in skeletal muscle cells.

Phytoestrogens

Phytoestrogens (plant estrogens) are compounds with a structural similarity to estradiol (E2), the primary female sex hormone. By binding to estrogen receptors (ERs), phytoestrogens can induce different biological activities asso-

TABLE 2. Diterpene contents in various coffee infusions*.

Coffee infusion type	Cafestol		Kahweol	
	(mg/L)	(mg per serving**)	(mg/L)	mg per serving**
Boiled	26–49	4–8	48.0+2.5	7.2
Espresso	22–30	1.0	16.3–17.1	1.0
Filtered	0.12+0.02	0.02	0.14+0.03	0.02
French press	29–53	5–9	–	–
Instant	0.7–1.9	0.1–0.3	0.7–1.9	0.1–0.3
Mocha	19–33	1–2	38.5+0.9	2.3
Turkish	23–41	1.4–2.5	89.9+4.1	5.4

*adopted from: [Zhang et al., 2012; Buchmann et al., 2011; Gross et al., 1997]; **serving size for coffee: boiled, 150–160 mL; French press 160 mL; filtered, instant 150 mL; espresso, mocha, Turkish 60 mL.

ciated with estrogenic or anti-estrogenic activity [Rietjens *et al.*, 2017].

Coffee contains rather small amounts of phytoestrogens, which belong to different classes of polyphenols, such as lignans and isoflavones. Ground coffee is a source of lignan secoisolariciresinol in average amounts of 5.61 mg/kg but does not contain matairesinol [Mazur *et al.*, 1998]. In a recent study, lignans found in espresso coffee prepared from coffee samples from 5 different geographical regions comprised secoisolariciresinol, from 27.9 to 52.0 $\mu\text{g/L}$, and lariciresinol, from 5.3 to 27.8 $\mu\text{g/L}$ [Angeloni *et al.*, 2018]. Again, matairesinol was not detected. Considering the consumption of lignans in the range of 1000–2000 $\mu\text{g/d}$ in European countries [Tetens *et al.*, 2013; Witkowska *et al.*, 2018], the usual daily coffee intake of 2–3 coffee cups may provide a mere 1.3–2.4% of total lignans. In the intestines, lignans are metabolized by anaerobic bacteria to enterolignans such as enterolactone and enterodiol, which demonstrate estrogenic activity [Zhu *et al.*, 2017]. Enterodiol was also found in coffee brews in amounts ranging from 97 to 135 $\mu\text{g/L}$ [Sapozhnikova, 2014].

Isoflavones found in coffee are mainly daidzein, genistein, and formononetin. In ground coffee, they account for 3.2–5.2 mg/kg, 0.9–1.4 mg/kg, and 3–6 $\mu\text{g/kg}$, respectively [Sapozhnikova, 2014]. Overall, isoflavone consumption in Europe has been described as low, and originated mainly from soybean products [Zamora-Ros *et al.*, 2012].

Chlorogenic, caffeic, and ferulic acids

Structurally, chlorogenic, caffeic, and ferulic acids are phenolic compounds that are classified as hydroxycinnamic acids (Figure 1). Ferulic acid (4-hydroxy-3-methoxy cinnamic acid) is synthesized in plants from caffeic acid (3,4-dihydroxycinnamic acid). Chlorogenic acid is an ester of caffeic and quinic acids (3-caffeoylquinic acid). In nature, there is a whole range of different derivatives of hydroxycinnamic acids, which are also typical of green coffee. They are intermediates in lignin biosynthesis. Hydroxycinnamic acids are ubiquitous in plant foods, but their significant amounts were also found in coffee. Therefore, coffee can be the main source of hydroxycinnamic acids in countries with high coffee intake [Witkowska *et al.*, 2015]. Caffeoylquinic acids, which are the main hydroxycinnamic acids in coffee, can vary in coffee infusions up to a wide range of 6–188 mg/cup [Jeon *et al.*, 2019; Ludwig *et al.*, 2014]. They have been ascribed various activities related to carcinogenesis. On the one hand, hydroxycinnamate demonstrates antioxidant, anti-inflammatory, antidiabetic, and antimicrobial potential [Teixeira *et al.*, 2013; Vinholes *et al.*, 2015]. But on the other hand, chlorogenic acid, caffeic acid, and caffeic acid phenethyl ester (CAPE) are *in vitro* inhibitors of catechol-*O*-methyltransferase (COMT)-mediated *O*-methylation of catechol estrogens to their less estrogenic derivatives [Zhu *et al.*, 2009]. This inhibition of COMT may lead to the reduced formation of antiproliferative 2-methoxyestradiol and increased accumulation of reactive catechol estrogen intermediates, which may affect cancer development. Interestingly, caffeic acid has been recently suggested as an enhancer of ovarian cancer cells' resistance to treatment [Sirota *et al.*, 2015].

Trigonelline

Trigonelline (*N*-methylnicotinic acid), a product of mammalian metabolism of niacin (vitamin B₃), is an alkaloid that also occurs in various plants. Its chemical structure is presented in Figure 1. After caffeine, it is the second most abundant alkaloid in coffee [Acidri *et al.*, 2020], with average concentration approximating 300 mg/L [Lang *et al.*, 2008]. During the roasting process, much of the trigonelline is degraded to nicotinic acid [Lang *et al.*, 2008].

Trigonelline may have estrogenic properties. In estrogen-dependent human breast cancer cells MCF-7, it has been reported to enhance cell proliferation, induce activation of estrogen response element (ERE), and activate ERs [Allred *et al.*, 2009].

Many compounds found in plants exhibit antioxidant properties. However, trigonelline was identified as a potent suppressor of the Nrf2/ARE pathway [Boettler *et al.*, 2011], which regulates the expression of genes involved in cellular antioxidant and anti-inflammatory protection. In turn, trigonelline degradation product, the *N*-methylpyridinium ion (NMP) – which is formed during the roasting process, has strong, long-lasting effects that enhance Nrf2/ARE-dependent gene expression [Boettler *et al.*, 2011].

Acrylamide

The most relevant dietary sources of acrylamide are solid coffee constituents, coffee, and fried potato products [EFSA Panel on Contaminants in the Food Chain (CONTAM), 2015; Freisling *et al.*, 2013]. Acrylamide molecules are formed in coffee beans during the process of roasting. The acrylamide content of coffee can vary greatly. In European countries, its average content in ground coffee was estimated at 225–231 $\mu\text{g/kg}$ (depending on the year of sampling), while the maximum value of up to 2223 $\mu\text{g/kg}$ [EFSA, 2011]. For instant coffee, these results were higher with an average value of 357–595 $\mu\text{g/kg}$ and a maximum value of 1470 $\mu\text{g/kg}$. The latest results of research conducted in Poland demonstrated its contents in the range from 61 to 397 $\mu\text{g/kg}$ in ground coffee and from 152 to 830 $\mu\text{g/kg}$ in instant coffee [Mojska & Gielecińska, 2013]. The average percentage exposure of adults across Europe to acrylamide from roasted coffee, as a proportion of total food intake, was estimated at 0.5–39.9% [EFSA, 2011; Mojska *et al.*, 2010]. The chemical structure of acrylamide is presented in Figure 1. In 1994, it was classified by the International Agency for Research on Cancer (IARC) as “probably carcinogenic to humans (group 2A)” [WHO, 1994], and this definition is still valid. In rodent studies, acrylamide administered in drinking water showed a dose-related carcinogenic potential by inducing mammary and ovarian tumors [Beland *et al.*, 2013]. In humans, dietary acrylamide exposure is much lower than this in animal studies, ranging from 12 to 39 $\mu\text{g/day}$ in European women [Freisling *et al.*, 2013]. Large cohort studies allowed concluding that the usual food intake does not seem to be associated with an increased risk of breast cancer [Kotemori *et al.*, 2018; Wilson *et al.*, 2009] or ovarian cancer [Larsson *et al.*, 2009; Obón-Santacana *et al.*, 2016] induced by acrylamide. Also, no associations have been found between the intake of food high in acrylamide, including coffee, and an increased risk

of premenopausal breast cancer development [Wilson *et al.*, 2009]. Still, associations between acrylamide and ovarian or endometrial cancers cannot be completely excluded among high acrylamide consumers [Hogervorst *et al.*, 2007; Pelucchi *et al.*, 2015; Wilson *et al.*, 2010].

COFFEE AND SEX HORMONES

The main female sex hormones are estrogen and progesterone. Natural estrogenic steroids are estrone (E1), estradiol (E2), and estriol (E3), of which estradiol is the most potent form. Ovarian-produced estradiol is the main estrogen in menstrual years, whereas estrone dominates in the menopause, produced in peripheral tissues from steroid precursor androstenedione. Unlike estriol, estrone can be converted to estradiol (Figure 2).

Estradiol exerts its biological effects through ERs located in the ovary, uterus, and breasts. Estrone and estradiol are hydroxylated by hepatic CYPs to catechol estrogen metabolites of various biological activities such as 2-pathway metabolites (2-hydroxyestradiol, 2-hydroxyestrone) and 4-pathway metabolites (4-hydroxyestradiol, 4-hydroxyestrone) (Figure 2). The 2-hydroxylated catechol estrogens are weak estrogens with potential anti-estrogenic activity [Ziegler *et al.*, 2015]. Hydroxylated catechol estrogens are metabolized in the liver by catechol *O*-methyltransferase (COMT) to methoxylated estrogens such as 2-methoxyestradiol, 2-methoxyestrone and 4-methoxyestradiol, 4-methoxyestrone. The 2-methoxyestradiol exhibits anti-angiogenic, pro-apoptotic, and antitumor activities [Aquino-Gálvez *et al.*, 2016; Gorska-Ponikowska *et al.*, 2017]. Furthermore, a 16-pathway metabolite – 16 α -hydroxyestradiol (estriol, E3) being a weak estrogen – is produced in small quantities in non-pregnant women *via* hepatic 16 α -hydroxylation of estradiol and estrone by CYPs.

A growing number of studies have shown that plasma estrogens, especially free estradiol, which is unbound to the main estrogen carrier — sex hormone-binding globulin (SHBG) — are strongly associated with the risk of breast cancer development, mainly in the postmenopausal but also in the premenopausal women [Endogenous Hormones

and Breast Cancer Collaborative Group, 2013; Folkler & Dowsett, 2013]. Only the free estradiol fraction, which is just a few per cent of the total plasma estradiol, can penetrate to a cell and stimulate steroid receptors. Conversely, estrogens transported by SHBG are in this bound form inactive, whereas increased SHBG concentrations are linked to the lower breast cancer risk.

Several studies provided evidence for associations between coffee or caffeine intake and sex hormone concentrations [Kotsopoulos *et al.*, 2009; Nagata *et al.*, 1998; Sisti *et al.*, 2015]. Kotsopoulos *et al.* [2009] found that the total and free luteal estradiol concentrations in premenopausal women were inversely associated with coffee and caffeine intake. In contrast, the progesterone level was positively associated with caffeine but not with the intake of coffee. In turn, in the postmenopausal women, caffeine and coffee consumption was positively related to SHBG level. No relationship was found between coffee, caffeine or decaffeinated coffee and the concentrations of androgens or prolactin. This result suggests that coffee and caffeine may favorably modulate estrogen metabolism and protect against breast cancer both in pre- and postmenopausal women, but the mechanisms of this protection are entirely different.

A recent study which used data from 587 premenopausal women, participants of the Nurses' Health Study II, demonstrated that the estrogen metabolism could be influenced by coffee intake and by caffeine [Sisti *et al.*, 2015]. This study measured mid-luteal urinary concentrations of 15 estrogens and estrogen metabolites and connected them to both caffeine and coffee intake ascertained on the basis of self-reported food frequency questionnaires. It was found that high (>4 cups/day) *versus* low coffee intake (<4 cups/week) was associated with higher excretion of 2-pathway estrogen metabolites of low estrogenic activity, *i.e.* 2-hydroxyestradiol and 2-hydroxyestrone. Conversely, the 2-pathway metabolism was not affected by the consumption of decaffeinated coffee. However, the intake of at least 2 cups of decaffeinated coffee per day was associated with a significant reduction of 16-pathway metabolites with estrogenic activity, *i.e.* estriol and 17-epiestriol (17 α -epimer of estriol), as compared to occasional coffee drinkers (<1–3 cups/month). In turn, higher caffeine intake was associated with higher urinary concentrations of 16 α -hydroxyestrone and 16-epiestriol. This study concluded that the consumption of caffeine and coffee may differentially alter patterns of estrogen metabolism in the premenopausal women.

COFFEE AND BREAST, ENDOMETRIAL, AND OVARIAN CANCERS IN WOMEN

In vitro, coffee brews and some compounds present in coffee demonstrate antiproliferative activities in cancer cells [Tai *et al.*, 2010]. Study results have shown that coffee compounds have an additive antiproliferation effect on cancer cell lines [Tai *et al.*, 2010]. It has been suggested that selected coffee secondary metabolites may beneficially modulate several mechanisms of anti-cancer protection.

A number of studies have demonstrated an inverse relationship between coffee consumption and cancer risk [Arthur

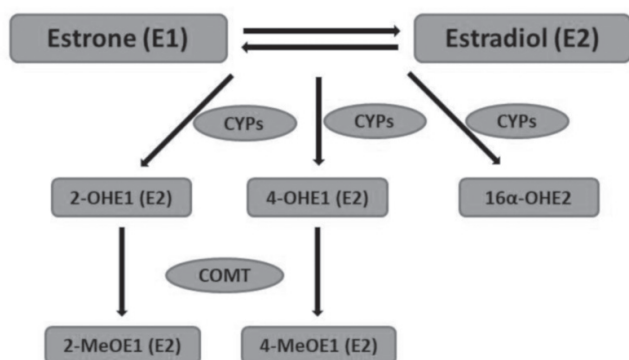


FIGURE 2. Metabolism of estrogen hormones. CYP – cytochrome P450, 2-OHE1 – 2-hydroxyestradiol, 4-OHE2 – 4-hydroxyestradiol, 16 α OHE2 – 16 α -hydroxyestradiol, 2-MeOE1 – 2-methoxyestrone, and 4-MeOE1 – 4-methoxyestrone.

et al., 2018; Oh *et al.*, 2015; Park *et al.*, 2018]. Recently, one study threw light on the nature of associations between coffee consumption and some markers of immune system activation that may have a role in the development of cancer and chronic diseases. It was found that heavy coffee drinkers had lower circulating levels of host response proteins (IFN γ , CX3CL1/fractalkine, CCL4/MIP-1 β), cell growth regulators (FGF-2), and proinflammatory cytokine sTNFR II than coffee abstainers [Loftfield *et al.*, 2015].

Although breast cancer occurs in both sexes, it is most common in women. The current state of knowledge about breast, endometrial, and ovarian cancers in the context of coffee intake is discussed below.

Breast cancer

Cancers of the mammary glands are the most common invasive female cancers worldwide, and are also the leading cause of all cancer deaths in women [Ferlay *et al.*, 2015]. The degree of morbidity increases with age and grows significantly after the age of 40. Breast cancer incidence is associated with both modifiable and genetic factors. The modifiable risk factors include being overweight or obese, physical inactivity, and alcohol use. As estimated, these factors together contribute to 21% risk of developing breast cancer [Danaei *et al.*, 2005]. The genetic factors are mostly associated with the presence of abnormal *BRCA-1* (breast cancer 1) and *BRCA-2* (breast cancer-2) genes, which are normally involved in DNA repairing processes [Ford *et al.*, 1998]. Mutations of these tumor-suppressor *BRCA* genes may lead to an increased risk of breast cancer development.

In the *BRCA-1* gene mutation carriers, high intake of caffeinated coffee amounting to 6 cups or more daily demonstrated a favorable effect by lowering breast cancer risk as compared to coffee abstainers [Nkondjock *et al.*, 2006], an effect not observed in *BRCA-2*. Recent research has indicated that coffee and/or caffeine might have a chemopreventive effect, regardless of whether the women had the *BRCA-1* gene or not [Nikitina *et al.*, 2015]. This effect was attributed to a more efficient repair processes of damaged DNA [Nikitina *et al.*, 2015]. On the other hand, excessive consumption of coffee could have adverse effects. In female non-carriers of abnormal *BRCA* genes, extremely large coffee consumption of 8 or more cups daily was associated with an increased risk of developing breast cancer [Bissonauth *et al.*, 2009].

In women with defective *BRCA-1*, a protective effect seems to be associated with a mechanism of caffeine elimination through cytochrome P450 1A2 (CYP1A2), which is also common for the metabolism of estrogen. The protective effect of coffee in the *BRCA-1* abnormal gene carriers was limited to those females who had at least one C variant of cytochrome CYP1A2 [Kotsopoulos *et al.*, 2007].

Until now, several dozen cohort and case-control studies have been devoted to the influence of coffee consumption on the incidence of breast cancer (Table 3). Most of the population studies showed no correlation between coffee drinking and breast cancer [Arthur *et al.*, 2018; Bhoo-Pathy *et al.*, 2010; Boggs *et al.*, 2010; Fagherazzi *et al.*, 2011; Gierach *et al.*, 2012; Grosso *et al.*, 2017a, b; Hashibe *et al.*, 2015; Lukic *et al.*, 2016; Yaghjian *et al.*, 2018], while some showed reduction

[Nilsson *et al.*, 2010; Oh *et al.*, 2015]. However, a 2018 dose-response meta-analysis of prospective cohort studies, which included more than a million women, showed that daily coffee consumption of 2 cups reduced the risk of breast cancer in postmenopausal women [Lafranconi *et al.*, 2018]. Similarly, the earlier meta-analysis of 37 case-control studies showed a negative trend in postmenopausal women [Jiang *et al.*, 2013].

Several studies assessed the risk of breast cancer based on the status of ER and progesterone receptor (PR). A Swedish *Women's Lifestyle and Health* cohort study demonstrated that coffee consumption and caffeine intake was negatively associated with the risk of developing ER positive and PR negative (ER+/PR-) breast cancer [Oh *et al.*, 2015]. In turn, in a European Prospective Investigation into Cancer and Nutrition (EPIC) cohort study, a linear trend was observed for a lower risk of postmenopausal breast cancer with increasing caffeinated coffee intake for ER-/PR- cancer [Bhoo-Pathy *et al.*, 2015]. Another Swedish study reported a lower risk of ER- breast cancer in postmenopausal high coffee consumers [Li *et al.*, 2011]. Furthermore, a study undertaken in Sweden, which involved 1090 patients with invasive primary breast cancer, shed light on the effects of coffee on cancer progression [Rosendahl *et al.*, 2015]. This study showed that smaller invasive primary tumors and lower prevalence of ER+ tumors were observed in moderate (2–4 cups/day) to high (>5 cups/day) coffee consumers compared to low (<1 cup/day) coffee consumers. Also, this moderate to high coffee intake was associated with a lower risk of breast cancer events in ER+ tumor patients treated with tamoxifen. These findings were translated into molecular and cellular levels [Rosendahl *et al.*, 2015]. Coffee contains several biologically active substances which may interact with breast cancer cells to impair their cell-cycle progression and increase cancer cell death. Two of them are caffeine and caffeic acid. Both seem to sensitize breast cancer cells to tamoxifen and suppress growth of ER+ and ER- cells [Rosendahl *et al.*, 2015]. In addition, caffeine reduces the number of ERs and cyclin D1 in ER+ cells, and also reduces insulin-like growth factor-1 receptor (IGF1R) expression, which is implicated in carcinogenesis of some tumors, including breast cancer, and phosphorylated Akt (pAkt) levels in both ER+ and ER- cells, the enzyme which contributes to poor prognosis in breast cancer.

Recently, there has been a report from a case-control study showing that instant coffee, unlike brewed coffee, can increase the risk of breast cancer development [Lee *et al.*, 2019]. This study concluded that there is a need for research on the effects of different types of coffee on the risk of breast cancer development.

Ovarian cancer

The number of studies on ovarian cancer and coffee and/or caffeine is steadily increasing. So far, several prospective cohort and case-control studies have been performed. Recently, two meta-analyses have been conducted, one concerning 8 prospective studies and the other – 20 case-control studies [Berretta *et al.*, 2018; Shafiei *et al.*, 2019].

Epidemiological studies are inconsistent in finding whether coffee, caffeine or decaffeinated coffee could be associated

TABLE 3. Studies between 2010–2019 on coffee/caffeine intake and the risk of breast cancer.

	Name and design of research	Total number of participants	Number of breast cancer (BC) cases	Major study outcomes	Reference
Coffee	EPIC-NL Cohort, Netherlands	27,323	681	No association between coffee consumption and BC risk.	Bhoo-Pathy <i>et al.</i> [2010]
Coffee, caffeine	Black Women's Health Study, USA, cohort study	52,062	1268	No association between coffee consumption or caffeine intake and BC risk among African-American women.	Boggs <i>et al.</i> [2010]
Coffee	Vasterbotten Intervention Project, Sweden, prospective cohort study	64,603	3034	Boiled coffee ≥ 4 versus < 1 intakes/day associated with a reduced risk of BC (HR = 0.52, CI 0.30–0.88, p (trend) = 0.247). Increased risk of premenopausal BC for total coffee (HR=1.69, CI 0.96–2.98, p (trend) = 0.015) and filtered coffee (HR= 1.76, CI 1.04–3.00, p (trend) = 0.045). Reduced risk of postmenopausal BC for total coffee (HR= 0.60, CI 0.39–0.93, p (trend) = 0.006) and filtered coffee (HR= 0.52, CI = 0.30–0.88, p (trend) = 0.045).	Nilsson <i>et al.</i> [2010]
Coffee, caffeine	E3N cohort, France	67,703	2868	No association between coffee consumption or caffeine intake and BC risk.	Fagherazzi <i>et al.</i> [2011]
Coffee, caffeinated, decaffeinated	Health-AARP Diet and Health Study cohort, USA	198,404	9915 (2051 ER+/PR+ and 453 ER-/PR- cancers)	No association between coffee, caffeinated and decaffeinated coffee and BC risk. No association with ER+/PR+ and ER-/PR- BC.	Gierach <i>et al.</i> [2012]
Coffee, decaffeinated coffee, caffeine	Metaanalysis of 37 case-control and cohort studies	966,263	59,018	No association between coffee consumption, decaffeinated coffee, caffeine and BC risk. An inverse weak association of coffee and caffeine with BC risk for postmenopausal women. Strong inverse association of coffee with BC risk for BRCA1 mutation carriers (RR=0.69, P<0.01).	Jiang <i>et al.</i> [2013]
Coffee, caffeinated coffee, decaffeinated coffee	European Prospective Investigation into Cancer and Nutrition (EPIC) cohort study	335,060	1064 premenopausal, 9134 postmenopausal	Caffeinated and decaffeinated coffee were not associated with premenopausal breast cancer. Caffeinated coffee associated with lower risk of postmenopausal breast cancer: adjusted HR=0.90, 95% CI, 0.82–0.98, for high vs. low consumption. Linear trend for lower BC risk with increasing caffeinated coffee intake most visible for estrogen and progesterone receptor negative (ER-PR-) postmenopausal breast cancer (P=0.008).	Bhoo-Pathy <i>et al.</i> [2015]
Coffee	Swedish Women's Lifestyle and Health prospective cohort study	42,099	1395	Decreased RR of BC for > 3–4 cups /day compared to 1–2 cups of coffee in pre- and postmenopausal women.	Oh <i>et al.</i> [2015]
Coffee, caffeine	Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer screening trial, USA	50,563	1698	No association between coffee consumption, caffeine and BC risk.	Hashibe <i>et al.</i> [2015]
Coffee	Norwegian Women and Cancer (NOWAC) Study, population-based prospective study	91,767	3277	No association between coffee consumption and BC risk.	Lukic <i>et al.</i> [2016]
Coffee	Cancer Prevention Study-II	922,896	6113	In nonsmokers, a 2 cup/day increase in coffee consumption inversely associated with death from BC (HR=0.97; 95% CI, 0.94–0.99).	Gapstur <i>et al.</i> [2017]
Coffee, caffeinated coffee, caffeine	Canadian Study of Diet, Lifestyle and Health (CSDLH), prospective case-cohort study	3120	922	Coffee and caffeine intake not associated with overall BC risk. Tendency towards increased BC risk with increasing levels of total coffee, caffeinated coffee and/or caffeine in premenopausal and normal weight women.	Arthur <i>et al.</i> [2018]
Coffee	UK Biobank	126,182 postmenopausal women	2,636	Coffee consumption not associated with BC risk (HR=1.00; 95% CI, 0.91–1.11 for 2–3 cups/day, and HR=0.98, 95% CI 0.87–1.10 for ≥ 4 cups/day. No significant interaction between postmenopausal hormone therapy and coffee consumption.	Yaghjian <i>et al.</i> [2018]
Coffee	Dose-response metaanalysis of prospective cohort studies	1,068,098	36,597	2 cups coffee/day associated with BC reduction in postmenopausal women (RR 0.90, 95% CI 0.82–0.99).	Lafranconi <i>et al.</i> [2018]
Coffee instant, coffee brewed	Case-control study in Hong Kong Chinese Women	2169	238	Instant coffee associated with increased BC risk (AOR = 1.50, 95% CI 1.10–2.03); brewed coffee negatively associated with BC risk (AOR = 0.48, 95% CI 0.28–0.82).	Lee <i>et al.</i> [2019]

BC – breast cancer; ER – estrogen receptor; PR – progesterone receptor; RR – relative risk; HR – hazard ratio; CI – confidence interval; AOR – adjusted odds ratio.

with the risk of ovarian cancer development. Research focuses on both, finding an increased as well as a decreased risk of developing ovarian cancer (Table 4). Some recent findings from the multinational EPIC cohort study, which included over 300,000 female participants, have shown increased mortality due to ovarian cancer in coffee drinkers [Gunter *et al.*, 2017]. The remaining studies point rather to a decrease [Gosvig *et al.*, 2015; Park *et al.*, 2018] or lack of associations with ovarian cancer risk [Arthur *et al.*, 2018; Berretta *et al.*, 2018; Braem *et al.*, 2012; Hashibe *et al.*, 2015; Leung *et al.*, 2016; Lukic *et al.*, 2016; Ong *et al.*, 2018; Shafiei *et al.*, 2019].

Ong *et al.* [2018] studied genetic predisposition towards higher coffee intake and its implications associated with the risk of epithelial ovarian cancer development. However, they did not confirm this relationship.

Interesting results concerning coffee and ovarian cancer risk are presented in a meta-analysis of 20 case-control studies [Shafiei *et al.*, 2019]. Although they did not establish any correlation between total coffee and caffeine intake, the authors found that decaffeinated coffee reduced the risk of ovarian cancer development. This may indicate an anticancer effect from other coffee ingredients than caffeine.

TABLE 4. Studies between 2010–2019 on coffee/caffeine intake and the risk of ovarian cancer.

	Name and type of research	Total number of participants	Number of OC cases	Major study outcomes	Reference
Coffee	European Prospective Investigation into Cancer and Nutrition (EPIC) prospective cohort study and metaanalysis	330,849	1244 EOC cases	No associations with EOC risk HR=1.05 (95% CI, 0.75–1.46) for the top quintile compared with no intake.	Braem <i>et al.</i> [2012]
Coffee, caffeine	Danish case-control study	1293	267 OC, 115 with borderline OC	Modest decrease in OC risk for coffee (OR = 0.90, 95% CI 0.84–0.97 per cup/day) and caffeine (from coffee and tea combined) (OR = 0.93, 95% CI 0.88–0.98 per 100 mg/day).	Gosvig <i>et al.</i> [2015]
Coffee, caffeine	Prostate, Lung, Colorectal, and Ovarian cancer screening trial, cohort study	97,334	162	No evidence of OC risk associated with coffee consumption. Suggested risk for caffeine intake for some specific OC quartiles.	Hashibe <i>et al.</i> [2015]
Coffee, caffeinated soft drinks	population-based Alberta and British Columbia, Canada case-control study	2111	524 EOC	No evidence for risk of EOC associated with coffee or caffeinated soft drinks.	Leung <i>et al.</i> [2016]
Coffee	Norwegian Women and Cancer (NOWAC) Study, population-based prospective study	91,767	446	No association with OC risk.	Lukic <i>et al.</i> [2016]
Coffee	EPIC (European Prospective Investigation into Cancer and Nutrition), prospective cohort study	321,081	848 OC deaths	Positive association between coffee and OC mortality (HR=1.12, 95% CI 1.02–1.23, P-trend 0.001).	Gunter <i>et al.</i> [2017]
Coffee, caffeinated coffee, caffeine	Canadian Study of Diet, Lifestyle and Health (CSDLH), prospective case-cohort study	2826	104	Coffee and caffeine intake not associated with OC overall risk.	Arthur <i>et al.</i> [2018]
Coffee, caffeine	Ovarian Cancer Association Consortium (OCAC), Europe	–	44,062 EOC	Single nucleotide polymorphisms (SNP) rs6968865 from the <i>AHR</i> gene and rs2472297 from the <i>CYP1A2</i> gene, associated with coffee consumption. No evidence on strong association between EOC risk and genetically predicted coffee or caffeine levels.	Ong <i>et al.</i> [2018]
Coffee	Multiethnic Cohort Study in Hawaii and Los Angeles, USA	167,720	1795	Reduced OC risk with HR = 0.33 (95% CI 0.17–0.65); P-trend = 0.007.	Park <i>et al.</i> [2018]
Coffee	Metaanalysis of 8 prospective cohort studies	787,076	3541	Coffee intake not associated with OC risk.	Berretta <i>et al.</i> [2018]
Coffee, caffeine, caffeinated coffee, decaffeinated coffee	Metaanalysis of 20 case-control studies	40,140	8568	No significant association between total coffee intake or caffeine and OC risk. Inverse association between decaffeinated coffee intake and OC risk (OR=0.72, 95% CI 0.58–0.90). No association with caffeinated coffee.	Shafiei <i>et al.</i> [2019]

OC – ovarian cancer, EOC – epithelial ovarian cancer, RR – relative risk, HR – hazard ratio, OR – odds ratio, CI – confidence interval.

Endometrial cancer

Endometrial cancer (EC) is the most common uterine cancer, which is derived from the endometrium, the inner lining of the uterus. The risk factors for endometrial cancer include obesity, long-term stimulation by increased levels of estrogen, high blood pressure, diabetes, early age of menarche, nulliparity, and late menopause [Ali, 2014; Raglan et al., 2019]. Postmenopausal women aged 60–70 years with excessive body weight are more predisposed to this cancer. After the menopause, gonadal production of estrogen and progesterone decreases, and androstenedione – another hormone produced by ovaries, is converted by adipose tissue to estrone in obese women. Continuous stimulation of endometrium by estrone without progesterone secretion leads

to uncontrolled proliferation of endometrial tissue [Michels et al., 2019]. Most cases of endometrial cancer fell into this cause-and-effect pattern (Type I EC); however, there are EC cases (10–20%) which are non-estrogen dependent (Type II EC) [Doll et al., 2008]. Whereas molecular characteristics describe Type EC I as endometrial endometrioid adenocarcinomas (EEAs) with or without squamous differentiation and in most cases well differentiated, whereas Type II tumors are high-grade serous papillary or clear cell carcinomas [Doll et al., 2008].

Relatively many studies concern the consumption of total coffee, caffeinated, and decaffeinated coffee, and caffeine in relation to the risk of EC (Table 5). At least five meta-analyses of cohort and case-control studies were carried out

TABLE 5. Studies between 2010–2019 on coffee/caffeine intake and the risk of endometrial cancer.

	Name and type of research	Total number of participants	Number of EC cases	Major study outcomes	Reference
Coffee, coffee caffeinated, coffee decaffeinated	Women's Health Initiative Observational Study, USA	45,696	427 postmenopausal women	No association between coffee consumption and EC risk. No associations among normal-weight and overweight women for total coffee and caffeinated coffee.	Giri et al. [2011]
Coffee, coffee caffeinated, coffee decaffeinated	Nurses' Health Study (NHS), USA	67,470	672	< 4 cups of coffee/day not associated with EC risk. Multivariable RR=0.75, 95% CI 0.57–0.97; P(trend) = 0.02) > 4 cups/day vs. > 1 cup/day. For ≥4 vs. <1 cup/d RR= 0.70, 95% CI = 0.51–0.95 for caffeinated coffee. For decaffeinated coffee consumption, a suggestive inverse association for 2 or more cups/day vs. <1 cup/month.	Je et al. [2011]
Coffee	Meta-analysis of 10 case-control and 6 cohort studies	–	6,628	For the highest versus lowest categories of coffee intake pooled RR=0.71 (95% CI 0.62–0.81; p for heterogeneity = 0.13) for EC. Pooled RR=0.69 (95% CI 0.55–0.87) for case-control studies and RR=0.70 (95% CI 0.61–0.80) for cohort studies. By geographic region, the inverse association was stronger for three Japanese studies (pooled RR=0.40, 95% CI 0.25–0.63) than five studies from USA/Canada (pooled RR=0.69, 95% CI 0.60–0.79) or eight studies from Europe (pooled RR=0.79, 95% CI 0.63–0.99). An increment of one cup per day of coffee intake conferred a pooled RR=0.92 (95% CI 0.90–0.95).	Je & Giovanucci, [2012]
Coffee caffeinated, decaffeinated, caffeine	Prospective cohort Iowa Women's Health Study (IWHs), USA	23,356	471 Type I, 71 Type II EC postmenopausal women	Type I EC (age range at diagnosis 57.2–89.5 years) significantly associated with caffeinated (RR=0.65 for 4+ cups per day vs. ≤ 1 cup per month, 95% CI 0.47–0.89), but not for decaffeinated coffee intake. No associations with tea, cola or chocolate, or for Type II EC. Inverse association with caffeinated coffee in women with BMI > 30 kg/m ² (RR=0.56; 95% CI: 0.36–0.89).	Uccella et al. [2013]
Coffee, caffeine	Swedish Women's Lifestyle and Health cohort study	42,270	144	Similar mean daily coffee consumption in women with and without EC (549 g vs. 547 g) and caffeine intake (405 vs. 406 mg). No association between coffee consumption or caffeine intake and EC risk among middle-aged women.	Weiderpass et al. [2014]
Coffee	Norwegian Women and Cancer (NOWAC) Study, population-based prospective study	97,926	462	Significant risk reduction found for ≥8 cups/day of coffee HR= 0.52 (95% CI 0.34–0.79) in multivariate adjustment model. No significant dose-response relationship. No significant heterogeneity in risk found for filtered and boiled coffee. Reduced EC risk in subgroup analyses among participants who drank ≥8 cups/day and had BMI ≥25 kg/m ² , and in current smokers.	Gavrilyuk et al. [2014]
Coffee, caffeine	Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer screening trial, USA	32,293	257	RR=0.69 (95% CI 0.52–0.91) for coffee intake ≥ 2 cups per day. Caffeine not associated with cancer risk in a dose-response manner.	Hashibe et al. [2015]
Coffee	UK Million Women prospective study and meta-analysis	560,356	4067	No significant association between EC risk and consumption of coffee. Weak association for coffee consumption with EC in prospective studies.	Yang et al. [2015]

TABLE 5. Continued

	Name and type of research	Total number of participants	Number of EC cases	Major study outcomes	Reference
Coffee	European Prospective Investigation into Cancer and Nutrition (EPIC) and Nurses Health Studies (NHS/NHSII)	539,237 (301,107 (EPIC); 238,130 NHS/ NHSII)	2834 (1303 EPIC; 1531 NHS/NHSII)	Multivariate-adjusted comparisons of extreme categories of intake: EPIC, median intake 750 g/day vs. 8.6 g/day; HR= 0.81 (95% CI 0.68–0.97), P _{trend} = 0.09; NHS/NHSII, median intake 1067 g/day vs. none; HR= 0.82 (95% CI 0.70–0.96), P _{trend} = 0.04.	Merritt <i>et al.</i> [2015]
Coffee, caffeinated coffee, decaffeinated coffee, caffeine	Dose-response meta-analysis of 13 prospective cohort studies	1,534,039	10,100	RR=0.80 (95% CI 0.74–0.86) for total coffee consumption (RR=0.60 (95% CI 0.50–0.72) in EC women never treated with hormones, R=0.57 (95% CI 0.46–0.71) in overweight/obese. Overall RR= 0.66 (95% CI 0.52–0.84) for caffeinated and RR=0.77 (95% CI 0.63–0.94) for decaffeinated coffee. Linear dose-response relationship for coffee, caffeinated coffee, decaffeinated coffee and caffeine intake. EC risk decreased by 5% for every 1 cup/day of coffee, 7% for every 1 cup/day of caffeinated coffee, 4% for every 1 cup/day of decaffeinated coffee, and 4% for every 100mg of caffeine intake/day.	Zhou <i>et al.</i> [2015]
Coffee	Dose-response meta-analysis of 12 prospective cohort studies	1,404,541	10,548	4 cups coffee /day associated with RR=0.80, 95% CI 0.72–0.89) for EC risk and with RR= 0.76, 95% CI 0.69– 0.83) for postmenopausal EC risk.	Lafranconi <i>et al.</i> [2017]
Coffee, caffeinated coffee, caffeine	Canadian Study of Diet, Lifestyle and Health (CSDLH), prospective case-cohort study	2608	180	For coffee cup increase HR=0.88 (95% CI 0.79–0.95), for caffeinated coffee cup increase HR=0.88 (95% CI 0.80–0.96), for 100mg caffeine increase HR=0.93 (95% CI 0.87–0.99).	Arthur <i>et al.</i> [2018]
Coffee	Meta-analysis of 12 cohort studies and 8 case-control studies	–	11,663 cases in cohort studies and 2,746 cases in case-control studies	For highest vs. lowest coffee intake summary RR= 0.74 (95% CI 0.68–0.81; p heterogeneity = 0.09, I ² = 32%), for cohort studies RR=0.78 (95% CI 0.71–0.85; p heterogeneity = 0.14, I ² = 31.9%), for case-control studies RR=0.63 (95% CI 0.53–0.76; p heterogeneity = 0.57, I ² = 0%). One-cup increment/day associated with 3% risk reduction (95% CI 2–4%) in cohort studies and 12% (95% CI 5–18%) in case-control studies. After pooling the results from 5 cohort studies that included BMI, the association remained significant only in women with BMI>30 (RR = 0.71, 95% CI 0.61–0.81).	Lukic <i>et al.</i> [2018]

EC – endometrial cancer, RR – relative risk, HR – hazard ratio, CI – confidence interval, BMI – body mass index.

between 2010 and 2019 [Je & Giovannucci, 2012; Lafranconi *et al.*, 2017; Lukic *et al.*, 2018; Yang *et al.*, 2015; Zhou *et al.*, 2015]. In cohort studies, high coffee intake compared to no intake was associated with a lower EC risk [Merritt *et al.*, 2015]. Similar findings were reported for coffee, caffeinated coffee, and caffeine [Arthur *et al.*, 2018]. Intake of four or more cups of coffee a day [Je *et al.*, 2011], or more recently consumption of two or more cups a day [Hashibe *et al.*, 2015], was associated with lower EC risk, but some research showed no conclusive association [Weiderpass *et al.*, 2014]. Coffee intake was found to be particularly beneficial in overweight or obese women [Friberg *et al.*, 2009; Gavriluk *et al.*, 2014; Lukic *et al.*, 2018; Uccella *et al.*, 2013; Zhou *et al.*, 2015]. Several studies have indicated that coffee intake might be associated with a decreased cancer risk in obese postmenopausal women [Giri *et al.*, 2011, Uccella *et al.*, 2013]. Caffeinated coffee consumption seems to have an advantage over decaffeinated coffee [Zhou *et al.*, 2015].

In one study, coffee was examined as a contributor to the dietary antioxidant activity (DAA) of EC patients. Coffee-related DAA was found to be inversely associated with the overall EC risk (OR=0.87, CI 0.77–0.99) [Rossi *et al.*, 2016]. Such association, however, was weak for DAA with no coffee intake included. The above research points to the role

of coffee as a dietary factor with the strongest impact on DAA, whereas the highest DAA quartile is associated with the lowest risk of EC (OR=0.75, CI 0.52–1.08).

The evidence supports the association between coffee and decreased EC risk in postmenopausal women. The mechanism of this association is not clearly understood. One line of evidence points to diabetes, which is a well-established factor in EC development. Most recently, the risk of developing EC has been linked to high fasting insulin, C-peptide and HOMA-IR values, which are the parameters used to assess β -cell function and insulin resistance [Hernandez *et al.*, 2015]. Coffee intake combined with hormone-replacement therapy (HRT) seems to sensitize cell receptors to insulin and decrease insulin resistance in postmenopausal women [Catalano *et al.*, 2008]. Insulin resistance correlates directly with body mass index (BMI), and coffee intake increases insulin sensitivity in overweight women [Catalano *et al.*, 2008].

CONCLUSIONS

As shown in publications cited in this paper, coffee is composed of multiple chemical compounds, that vary according to such factors as: type of beans (Arabica, Robusta), roasting process, preparation (instant coffee) and brewing

method. Therefore, their content in a coffee cup can vary greatly. Most long-term observational studies were planned from the viewpoint of consumption of total, caffeinated, decaffeinated coffee, and caffeine, but they took no account of the size of coffee portions and the content of biologically active substances, which may vary several times between cups. Such studies generally do not distinguish between ground roasted coffee and instant coffee. A recent case-control study has raised this issue and showed a positive relationship with breast cancer [Lee *et al.*, 2019]. For all these reasons, it is difficult to determine the appropriate dose and type of coffee that would be most effective in preventing cancer. An issue that has not yet been studied is the question of the additives with which coffee is consumed, such as milk or sugar, and how they can affect bioavailability of coffee compounds, as has been shown for tea [Korir *et al.*, 2014]. Clinical trials offer more standardized conditions of research. However, in the case of cancer, long-term clinical trials are not feasible. In turn, long-term observational studies are in some cases ambiguous as regards the effect of coffee consumption, showing a positive, negative or no relationship between coffee consumption and breast, ovarian or endometrial cancer. In general, most studies and meta-analyses indicate that there is no clear correlation between coffee and breast cancer or ovarian cancer. However, some subgroups of women can benefit from coffee consumption. This is the case for post-menopausal women with regard to the risk of breast cancer and obese women with regard to the risk of endometrial cancer [Lafranconi *et al.*, 2018; Lukic *et al.*, 2018; Zhou *et al.*, 2015]. The situation is unclear in the case of ovarian cancer, where the effect of coffee is generally not observed, but in the case of decaffeinated coffee the opposite relationship may exist [Shafiei *et al.*, 2019]. Further research should therefore be targeted at them with clearly defined portion sizes and preparation methods. In addition, more attention should be paid to whether or not cancer is hormone-dependent and whether there is a genetic predisposition to breast, ovarian or endometrial cancer. Many lifestyle factors such as smoking, improper diet, excessive consumption of alcohol, contribute to the risk of developing cancer. Future research should pay attention to selecting participants in order to minimize the possible influence of confounding factors [Grosso *et al.*, 2016].

Coffee is an important dietary source of biologically active compounds with the caffeine being the most abundant. *In vitro* and *in vivo* studies suggest that various classes of secondary metabolites of coffee may beneficially modulate several mechanisms of anti-cancer protection. It would be interesting to examine whether the compounds present in coffee have a synergistic effect and whether caffeine is indeed one of the most important substances that have an anti-cancer effect. Recent studies show that decaffeinated coffee can also exhibit these properties [Shafiei *et al.*, 2019], indicating that other coffee compounds are important as well. The available literature on human studies related to single coffee components is limited to caffeine and therefore this research topic is needed to be developed. Furthermore, the metabolism of many coffee compounds in the body requires better characterization. This applies especially to phenolics, which undergo microbiologi-

cal transformation in the intestine. And yet, some coffee compounds, such as lignans and trigonelline, have an estrogenic activity, which can be important when studying hormone-dependent cancers.

There are some strengths and limitations of this review. Its strength and at the same time its limitation is the time-period in which literature was sought, which allowed for the collection of the latest publications, but omitted most of the publications before that period. However, in the case of observational studies, most of the previous case-control and epidemiological studies have been analyzed in recent meta-analyses. On the other hand, the search was limited to two electronic databases, thus some studies may not have been included in this review.

This literature review shows that, despite extensive knowledge of coffee and its effects on human health, there are still many open questions to explore in relation to breast, ovarian, and endometrial cancer. Important issues for future research are to better understand the anti-cancer mechanisms of coffee compounds, especially of diterpenes, trigonelline and phenolics, and to undertake research that would focus on specific target groups, taking into account both the different methods of coffee preparation and lifestyle factors that may interfere with the results.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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