5. SUMMARY OF DATA REPORTED

5.1 Exposure data

Coffee as a beverage has been consumed in many parts of the world for centuries. Coffee is prepared from the fruit seeds (called beans) of several species of the genus *Coffea* L. (Rubiaceae family). The two main types of cultivated coffee are commonly called Arabica and Robusta. After harvesting, the fruits are processed to obtain the beans which are then roasted and ground before brewing. There are variations in the way each of these steps are conducted, depending on the local farmer, industry, and consumer preferences. The quality and chemical composition of the beans can be affected at all stages of the processing.

The chemical composition of the beverage varies depending on the ratio of coffee to water, particle size, duration of brewing, percolation pressure, and filtration. Coffee contains compounds numbering several hundred. The concentration of caffeine, one of the major pharmacologically active compounds, is highly variable due to various factors such as coffee tree species and preparation method (average, 0.4 g/L). Decaffeinated coffee is also produced. Heat-induced contaminants such as acrylamide and furan regularly occur in coffee beans and brewed coffee.

Coffee production and consumption were both estimated to be about 9 million tonnes worldwide in 2015. Together, the European Union countries account for 28% of consumption; major individual consuming countries are the USA (16%), Brazil (13%), Japan (5.6%), and the Russian Federation (2.2%). In terms of per capita consumption, European countries are the major consumers. At an individual consumer level, there exists an extremely large variation in frequency of coffee drinking and portion size. Consumption has been stable in countries with high per capita consumption and has increased in countries that are currently lower per capita consumers; the latter countries are mainly situated in Africa, Asia, and Oceania.

Questionnaires used to assess coffee consumption vary in several ways, including: methods of dietary assessment and/or measurement used; whether questionnaires are validated/calibrated; differentiation between caffeinated and decaffeinated coffee; method of preparation; inclusion of serving or portion sizes; and ability to assess intake in terms of grams or litres per day.

5.2 Human carcinogenicity data

5.2.1 Bladder

In 1991 (*IARC Monographs* Volume 51), the Working Group concluded that there was limited evidence for the carcinogenicity of coffee drinking in humans. This evaluation was based on an increased risk of cancer of the bladder that was observed in several hospital-based case–control studies, with few cohort studies available. Two concerns with these older case–control studies are: (1) that coffee-drinking habits were assessed after case diagnosis and could be affected

by development of bladder cancer; and (2) the use of hospital-based controls in the majority of studies, with often unreported conditions that may affect coffee drinking, which can in turn introduce bias in reported coffee drinking and a subsequent overestimation of the risk. Bias in the observed estimates could therefore not be ruled out. Several large prospective cohort studies and population-based case–control studies have been published since 1991, with adjustment for tobacco smoking and/or results in non-smokers, and were available for this updated review.

The current Working Group examined the association between coffee intake and risk of cancer of the bladder in nearly 80 cohort and case–control studies conducted in Asia, Europe, South America, and the USA. In evaluating the evidence from these epidemiological studies, the Working Group placed the greatest weight on the cohort studies. This evaluation was complemented with information from population-based case–control studies, which were considered more informative than hospital-based studies. Studies that did not consider smoking as a confounder were excluded from evaluation.

Eleven cohort studies from Europe, Japan, and the USA reported on the association between coffee drinking and risk of cancer of the bladder with inconsistent results. There was no consistent evidence of a positive or inverse dose–response relationship with the quantity of coffee consumed. Within the studies that reported sex-specific results, associations among women were generally null or inverse and more often positive among men. The findings among women are particularly informative, in that those associations are less likely to be confounded by smoking and occupational exposure compared with associations among men. Of the two cohort studies that reported on non-smokers, one reported a non-significant positive association and the other a non-significant inverse association. Both were based on very small numbers of non-smokers.

Among the 14 independent population-based case–control studies, the findings were also inconsistent. Increased risks were reported in several studies, mostly among men. Modest positive associations were observed in several studies of non-smokers, but none were statistically significant.

In conclusion, there was no consistent evidence of an association or dose–response relationship between coffee drinking and cancer of the bladder. The majority of positive studies did not adequately adjust for smoking, and studies among non-smokers were limited by small sample size. Moreover, most studies did not adjust for occupational exposures. Sex-specific associations were more often positive among men. Among women, where confounding by occupational exposures and smoking is less likely, the associations were generally null or inverse. Residual confounding by smoking or occupational exposure therefore cannot be ruled out.

5.2.2 Pancreas

Evidence of the association between coffee drinking and cancer of the pancreas was available from 20 cohort studies and 22 case–control studies that controlled for smoking, of which 14 were population-based and 8 hospital-based. The review of epidemiological studies was restricted to those that adjusted for smoking. Cohort studies and population-based case–control studies, adjusting for multiple confounders, showed no overall association with total coffee drinking or with decaffeinated coffee drinking. The most important set of studies on which this conclusion is based is a pooled analysis of cohort studies with comparable methodology which found no association, including in non-smokers. A high-quality meta-analysis also showed no association with coffee intake in cohort studies or in case–control studies that adjusted for smoking. Several large cohort studies published after this meta-analysis

similarly found null associations. Overall, based on many large studies, there is no evidence of an association between coffee drinking and risk of pancreatic cancer.

5.2.3 Liver

A total of 14 cohort studies and 11 case–control studies conducted in Asia, Europe and North America examined the association between coffee consumption and the risk of cancer of the liver. All cohort studies adjusted for smoking and alcohol intake and, where possible, for hepatitis virus infection status and diabetes. All cohort studies observed inverse associations, which were statistically significant in most studies. Separate analyses by sex and by hepatitis C virus and/or hepatitis B virus infection status yielded similar results. Most case–control studies also observed inverse or null associations. In a 2015 pooling project of cohort studies in the USA (over 860 cases of hepatocellular carcinoma), the risk in the highest compared with the lowest category of coffee consumption was reduced by about 25%. The Working Group concluded that a consistent, statistically significant, inverse association between coffee drinking and risk of liver cancer has been observed in multiple studies.

5.2.4 Breast

Evidence of the association between coffee consumption and risk of cancer of the breast was available from 23 cohort and 22 case–control studies. Most of the reviewed studies showed no association, and several reported statistically significant inverse associations between coffee intake and breast cancer overall or among subgroups of premenopausal or postmenopausal women. The most recent meta-analysis of about one million women and more than 50 000 breast cancer cases reported a modestly decreased risk for the highest compared with lowest levels of coffee consumption, with an indication of an inverse dose–response relationship. Studies published after this meta-analysis reported null or inverse associations overall and among postmenopausal women. An inverse association was also observed in the recent large cohort study (2016). Inverse associations were reported in a small number studies among women with *BRCA1* mutations. One population-based case–control study among non-carriers of *BRCA1/2* mutations reported a positive association.

5.2.5 Uterus (endometrium)

Evidence of the association between drinking coffee and risk of endometrial cancer was available from 20 informative studies (12 cohort and 8 case–control studies) where body mass index and smoking were taken into account. Evidence from four of the largest cohort studies (the Swedish Mammography Cohort, the National Institutes of Health–American Association of Retired Persons (NIH-AARP) Diet and Health Study, the Nurses' Health Study (NHS) and NHS II, and European Prospective Investigation into Cancer and Nutrition (EPIC)) with over 6000 cases showed an inverse association with coffee drinking. The Million Women Study, including another 4000 cases, found a null association. Evidence from case–control studies is consistent with that of cohort studies, suggesting an inverse or a null association. A meta-analysis published in 2012 found a 30% lower risk of endometrial cancer among coffee drinkers, consistent with the majority of cohort and case–control studies.

5.2.6 Prostate

Evidence from ten cohort studies and four case–control studies of the association between coffee drinking and cancer of the prostate was evaluated. The greatest weight was given to studies of aggressive and fatal prostate cancer to reduce the potential for bias from screening. No case–control or cohort studies found positive

associations with the risk of total prostate cancer. Recent meta-analyses of cohort and case–control studies estimated inverse associations for fatal prostate cancer and no association for advanced prostate cancer. Studies conducted worldwide consistently indicated no increased risk of prostate cancer associated with coffee drinking, with inverse or null associations observed in all studies.

5.2.7 Oral cavity and pharynx

Evidence of the association between coffee drinking and cancers of the oral cavity and/or pharynx was available from more than 20 cohort and case–control studies in Europe, Japan, and the USA. Inverse associations were observed in the majority of informative studies, and these were statistically significant in about one half of the studies. An inverse dose–response relationship was also seen in a recent pooled analysis of case–control studies, as well as in four meta-analyses of cohort and case–control studies. Although data from several studies that combined results for the oral cavity and pharynx were suggestive of inverse associations, the Working Group concluded that these tumours are distinct entities and that the available data do not permit conclusions to be drawn about either cancer site.

5.2.8 Childhood leukaemia

Seven case–control studies have reported on the association between maternal coffee consumption during pregnancy and the risk of childhood leukaemia. The Working Group considered that the earliest two studies were of limited quality due to low participation fractions and uninformative exposure categories. Four of the remaining studies were conducted in France by the same research group (with no overlap of study populations). The first of these was hospital based and reported an increased risk with a significant dose–response trend. A second study by this team 2 years later used a population-based approach and reported an odds ratio slightly and non-significantly above unity. The third French study showed an increased risk with a significant dose–response trend, while the results of the fourth study were largely null. An Australian study found no evidence of an increased risk. The most recent meta-analysis of this association reported an overall increased risk for high levels of coffee consumption, but was limited by the fact that the highest exposure level varied widely across studies (from ≥ 4 times per week to ≥ 8 times per day). The lack of consistency among the findings of the studies, particularly those conducted within the same country by the same group, led the Working Group to evaluate the evidence for this site as inconclusive.

5.2.9 Lung

More than 20 cohort and case–control studies have reported on the association between coffee consumption and risk of lung cancer. Only studies that controlled for smoking were reviewed, but the level of adjustment for smoking was nevertheless inadequate in most of the older studies. Four recent large-scale studies (three cohort studies and one large population-based case–control study) performed careful adjustment for smoking. Positive associations between lung cancer and coffee drinking were substantially attenuated after these adjustments; they remained positive in the cohort studies, however, while they became null in the case–control study. In the most recent meta-analysis, coffee drinking was not associated with lung cancer when smoking was controlled. Among non-smokers, cohort, case–control studies and a meta-analysis did not find an association between coffee drinking and lung cancer. The Working Group concluded that the positive association between coffee drinking and lung cancer observed in some studies was probably explained by residual confounding due to smoking.

5.2.10 Larynx

Associations between coffee drinking and cancer of the larynx were evaluated in seven case–control studies, including a large pooled analysis, and one cohort study. The results of these studies were inconsistent. A significantly increased risk was observed in four case–control studies, but none of these studies had adequately controlled for smoking and alcohol use. No evidence of an association was observed in studies that tightly controlled for smoking and alcohol drinking, or in the pooled analysis of case–control studies. No evidence of excess risk of laryngeal cancer among coffee drinkers was observed in the prospective cohort.

5.2.11 Ovary

The evidence for the relation between coffee consumption and risk of cancer of the ovary is based on some 10 cohort and about 20 case–control studies. Evidence from the majority of the cohort studies, including the largest one and a meta-analysis, suggests no association. The evidence from case–control studies is inconsistent; although the majority of studies suggest a null association, some others show (mostly non-statistically significant) positive associations. Given the inconsistency of the results among studies, the Working Group found the evidence to be inconclusive.

5.2.12 Stomach

A total of 12 cohort studies and 14 case–control studies of the association between coffee drinking and gastric cancer reported inconsistent results, with no consistent evidence of a positive or inverse association between coffee intake and gastric cancer observed.

5.2.13 Oesophagus

Data on the association between coffee drinking and cancer of the oesophagus were available from three adequate cohort studies and eight case–control studies conducted in Europe, Asia, and the Americas that adjusted for tobacco smoking and alcohol drinking. Virtually all of these studies observed no association between coffee drinking and the risk of cancer of the oesophagus. One cohort study from Japan observed an inverse association with borderline statistical significance. No notable differences were observed between squamous cell and adenocarcinomas of the oesophagus. The two most recent case–control studies observed decreased risk. Two meta-analyses also suggested no association between coffee intake and oesophageal cancer.

5.2.14 Kidney

For renal cell carcinoma, four cohort studies (including a pooled analysis of prospective cohort studies) and five case–control studies were considered informative. The largest study pooled data from 13 prospective cohorts and found no overall association; significant inverse associations among women and among never-smokers were observed, with comprehensive adjustment for confounders. One large, well-conducted population-based case–control study found a significant positive association, and the remaining studies were either null or significantly inverse.

For renal pelvis cancer, only two population-based case–control studies were considered informative. Neither found a significant association between coffee intake and risk of renal pelvis cancer; however, confidence intervals were wide and there was limited adjustment for confounding.

5.2.15 Colorectum

Approximately 50 prospective cohort, case–control, and pooling studies have been conducted to evaluate the association between coffee drinking and cancer of the colorectum. Ten cohort studies that were considered to be the most informative, with case numbers in the hundreds to over one thousand, found null associations between coffee consumption and colorectal cancer. Three cohort studies found an increased risk of either colon or rectal cancer. A pooled analysis of 13 cohort studies of colon cancer (over 5600 cases) found no association. Two subsequent large cohort studies conducted in the USA and Europe found inverse and null associations of colorectal cancer with coffee drinking, respectively. The findings from case–control studies were mixed, with inverse associations in most studies and positive or null associations in others.

5.2.16 Skin

Thirteen studies – seven cohort studies and six case–control studies – reported inconsistent results for an association between coffee consumption and risk of cutaneous malignant melanoma. Of the cohort studies, four reported largely null findings while three reported inverse associations. In both of the cohort studies that presented results for men and women separately, the risk ratios for coffee drinking were significantly decreased for women and non-significantly increased for men. Of the case–control studies, four reported no association while two reported reduced risks with increased coffee consumption. A meta-analysis of these studies reported summary risk ratios for the highest versus lowest category of coffee intake that were significantly reduced among women and non-significantly elevated among men. Three cohort studies and three case–control studies have reported on the association between coffee consumption and risk of non-melanoma skin cancer. All of the studies reported null or inverse associations with coffee drinking.

5.2.17 Other cancer sites

Associations between coffee drinking and all cancers combined and cancers at several other sites – including Wilms tumour, brain cancer (in both adults and children), lympho-haematopoietic cancer in adults, cancers of the gallbladder and biliary tract, cancers of the small intestine, vulva, testis and thyroid, soft-tissue sarcoma, and breast cancer in men – were examined in only a few studies for each cancer site. The sparse evidence available for these cancers did not permit conclusions to be drawn.

5.3 Animal carcinogenicity data

Chronic studies to evaluate the potential carcinogenicity of coffee have been performed in male and female mice in one study (by transplacental/perinatal exposures followed by feeding), and in male and female rats in two studies (one feeding study and one study by transplacental/perinatal exposures followed by exposure to coffee-containing drinking fluid).

In the transplacental/perinatal/feeding study in mice, females exposed to coffee demonstrated a significant trend towards increased incidence of uterine leiomyoma. By contrast, coffee exposure was associated with significant, dose-related reductions in the incidences of total tumours and malignant tumours in both sexes. Significant and dose-related reductions in lymphosarcoma incidence were seen at several sites in both sexes, and males exposed to coffee also demonstrated a significant, dose-related reduction in the incidence of hepatocellular adenoma.

In the feeding study in rats, the animals fed caffeinated coffee or decaffeinated coffee plus caffeine demonstrated fewer tumours than sex-matched controls. A significant increase in

the total number of malignant tumours was seen in one group of females fed caffeinated coffee; however, since this increase was not seen in another group of females receiving comparable exposure to coffee, the Working Group interpreted it as an isolated and not reproducible finding.

In the transplacental/perinatal/drinking-fluid study in rats, the incidence of skin fibrosarcoma or squamous cell carcinoma (combined) was significantly increased in males given a low dose, but not in the groups receiving a medium or high dose. However, the individual incidences of skin fibrosarcoma and skin squamous cell carcinoma did not differ from controls in any dose group. No significant increases in total tumour incidence were seen in rats exposed to coffee. Significant decreases in the incidences of mammary gland fibroadenoma were seen in females exposed to coffee.

Coffee was tested for carcinogenicity in initiation–promotion or co-carcinogenicity studies as either: brewed or instant coffee in male or female rats by oral administration in the drinking fluid in seven studies; or as green beans, pressed oil from green beans, or a lyophilized roasted coffee extract in male or female rats by oral administration in the feed in three studies. Coffee was also tested as brewed coffee in one drinking-fluid study and one gavage study in male hamsters, and as green beans in one feeding study in female hamsters. These studies were designed to investigate the potential of coffee to mitigate the effect of different known carcinogens; because of the potency of the carcinogen used, these studies were often of relatively short duration or used small numbers of animals.

Of the 13 studies reviewed, only one reported a significant increase in tumours. When 2-acetylaminofluorene was used as an initiator and coffee used as a promoter in a drinking-fluid study, there was a significant increase in the incidence of adenocarcinomas of the mammary gland in female rats. In seven of the rat studies and one of the hamster studies, coffee caused a significant reduction in the incidence and/or multiplicity of the tumours induced in various organs by the different carcinogens; the organs included the mammary gland (two studies), liver (three studies), pancreas (one study), and colon (one study) in rats, and the buccal pouch (one study) in hamsters.

5.4 Mechanistic and other relevant data

Coffee has many constituents and numerous studies have examined their pharmacokinetics. After oral administration of coffee, absorption of caffeine, trigonelline, diterpenes, chlorogenic acids, and related compounds (hydroxycinnamates) occurs within hours and is dependent upon compound and dose. An in vivo study in mice showed that cafestol is efficiently absorbed. Upon ingestion of coffee, the major hydroxycinnamic acids that were identified in the plasma of humans were 5-*O*-caffeoylquinic acid and ferulic acid. For trigonelline, absorption is faster in women than in men. In human in vivo studies, the distribution of caffeine varies significantly with body weight and fat mass, but is not dependent on either the dose or the formulation. Trigonelline and related compounds have a high volume of distribution in humans consuming coffee.

The metabolism of caffeine in humans is rapid and dependent upon dose, with higher doses resulting in the formation of other methylxanthines. In vivo human studies reported interethnic differences in caffeine metabolism, in which multiple enzymes are involved. The main metabolic pathway in humans is CYP1A2-catalysed 3-*N*-demethylation. Smoking and heavy coffee drinking induce caffeine metabolism. The main metabolic pathway in rats is 8-hydroxylation, also mediated by CYP1A2. For hydroxycinnamic acids, sulfation is the main

conjugation pathway and more than 30 different derivatives were identified in humans. In mice, the major metabolite of cafestol is a glucuronide conjugate. Studies in rodents demonstrated that hydrolysis of chlorogenic acid can occur in the stomach and gut mucosa.

Multiple human studies showed induction of CYP1A2 as a consequence of coffee consumption. In addition, increased activity of GSTP but not GSTT was observed. Contrary to studies in humans in vivo, coffee and its constituents directly inhibit multiple enzymes in vitro, including CYP1A2, CYP3A4, CYP2B6, sulfotransferases (SULT), and catechol-*O*-methyltransferase (COMT); however, UDP-glucuronosyl transferases (UGT) was observed to be upregulated. In both rats and mice, coffee induces several metabolizing enzymes in many tissues. Coffee constituents may have opposing effects on the induction of metabolizing enzymes.

Human in vivo data showed that the elimination of caffeine and hydroxycinnamic acids is dose dependent, with higher doses associated with decreases of caffeine clearance. The extent of trigonelline elimination after coffee consumption is lower in women compared with men. 5-*O*-caffeoylquinic acid and 4-*O*-caffeoylquinic acid were the only unmetabolized hydroxycinnamic acids detected in the urine of humans after coffee consumption, whereas the most abundant phenolic acids were gallic and dihydrocaffeic acids. In studies in humans in vivo, kahweol and cafestol were eliminated in the urine and faeces. A study in rats in vivo reported efficient elimination of cafestol through bile.

With respect to the key characteristics of carcinogens, there is *weak* evidence that coffee drinking induces oxidative stress. Findings in humans in many studies of various designs, including randomized controlled trials, consistently demonstrated no effects. A variety of end-points have been evaluated. An exception is the increase of H_2O_2 in urine after consuming coffee, found in three acute interventions. In two studies in human intestinal cells in vitro, no pro-oxidant activity was detected. In lymphocytes directly exposed to coffee without metabolic activation, increased oxidative DNA damage was found. One study in rats detected increased excretion of 8-hydroxydeoxyguanosine (8-OHdG) but not F2-isoprostanes in urine upon exposure to high doses of coffee for up to 130 days. Several other studies in rats of shorter duration or of co-exposures to other oxidative stress-promoting factors showed protection by coffee on oxidative stress markers.

There is *strong* evidence that coffee drinking induces antioxidant effects. Largely consistent protective effects were seen in many human studies of various designs, including randomized controlled trials. Some of these studies examined antioxidant status while others demonstrated a general reduction in oxidative stress markers. Similar antioxidant properties of coffee were demonstrated in studies using human intestinal cell lines and lymphocytes. In several studies of short-term exposures in experimental animals, increased antioxidant enzyme activity, glutathione, and sulfhydryls in liver or plasma have been reported. Coffee induces activity of nuclear factor-erythroid-2-related factor (Nrf2). Finally, many different assays in cell-free systems of both coffee and its constituents demonstrated free radical scavenging activity.

There is *weak* evidence that coffee drinking induces chronic inflammation. In many human studies of various designs, including randomized controlled trials, coffee drinking had no consistent effect on proinflammatory markers C-reactive protein (CRP) and interleukin-6 (IL-6). In rodent models of proinflammatory conditions, coffee induced anti-inflammatory cytokines and suppressed the activation of NF-κB.

There is *weak* evidence that coffee drinking is genotoxic. The few studies in humans that have reported chromosomal damage in coffee drinkers have limitations in study design or

else present conflicting results. Some studies found protective effects of coffee drinking on oxidative DNA damage or strand breaks in lymphocytes; however, some studies showed no effect, or suggested that coffee drinking may be associated with genetic alterations in lymphocytes and sperm cells. In human cells, results in vitro are conflicting. Studies in rodents in vivo have shown no evidence that coffee induces chromosomal damage. Furthermore, many studies demonstrated protective effects of coffee towards genotoxicity induced by several carcinogens in many organs. There is some evidence in mammalian cells in vitro for induction of sister-chromatid exchanges after exposure to coffee; however, consistent negative findings were reported for micronuclei and in the comet assay. Bacterial mutagenesis assays with various coffee brews are consistently positive in absence of metabolic activation. In these experiments, formation of hydrogen peroxide from coffee is one likely mechanism for these effects as addition of antioxidants or antioxidant enzymes reduced the bacterial mutagenic effects of the brews. Another mechanism of mutagenesis in bacterial systems is through the effect of methylglyoxal, a substance that is present in coffee brews and other food products and beverages.

There is *weak* evidence that coffee constituents alter DNA repair or cause genomic instability. In the few available studies in vitro, caffeine inhibited several DNA repair pathways. One study in rats showed the induction of O^6-methylguanine-DNA methyltransferase (MGMT) in liver by kahweol and cafestol. There are no studies of coffee drinking and this key characteristic.

There is *weak* evidence that coffee constituents induce epigenetic alterations. In one study in human cell lines, caffeic and chlorogenic acids induced promotor demethylation of the retinoic acid receptor β. In three studies in rats, caffeine administration to pregnant dams reduced methylation of DNA and histones and induced expression of DNA methyltransferases and histone deacetylases in various tissues in the offspring. In one study in mouse myoblasts, caffeine induced hyperacetylation of histone H3. There are no studies of coffee drinking and this key characteristic.

There is *weak* evidence that coffee consumption alter cell proliferation, and there is moderate evidence that coffee consumption increases cell death through apoptosis. One intervention study in humans found that consuming large quantities of coffee had no effect on cell proliferation in colorectal mucosa. In many human cancer cell lines, coffee and coffee constituents exerted antiproliferative and proapoptotic effects. There is some evidence in humans and animals in vitro for antiangiogenic effects for the coffee constituents caffeine, cafestol, and kahweol. Two rodent studies of oral ingestion of coffee or caffeine reported increased cell proliferation in urinary bladder and ventral prostate, whereas another study showed a suppressive effect using a tumour-implant model. One study of short- or long-term oral administration of regular or decaffeinated coffee demonstrated increased autophagy in multiple organs, including liver, heart, and muscle.

There is *weak* evidence that coffee consumption modulates receptor-mediated effects. In several studies in human cells in vitro, coffee and coffee constituents had a direct stimulatory effect on nuclear receptors, including aryl hydrocarbon receptor (AhR), farnesoid X receptor (FXR), and pregnane X receptor (PXR). Increased levels of sex hormone-binding globulin (SHBG) were seen in coffee-consuming postmenopausal women and in men; however, results were inconsistent with respect to effects on androgens and estrogens. There is some evidence in humans in vivo and in vitro that coffee can modulate estrogen metabolism. Coffee modulates plasma levels of cortisol in both humans and rats, and a similar effect was observed in human cells in vitro. Studies in humans in vivo and human cells

in vitro and animals in vivo showed that coffee and coffee-derived phenolics stimulate excretion of gastrin and other gastrointestinal hormones. There is a positive association between coffee consumption and plasma adiponectin levels in humans. Coffee consumption lowers leptin in plasma in humans.

Coffee and/or caffeine preference is a highly heritable trait. Several large-scale genome-wide association studies (GWAS) and meta-analyses point to a small number of alleles, most notably polymorphisms in *AHR* and *CYP1A* genes, that are very strongly and consistently associated with the patterns of coffee consumption. A small number of studies examined genetic modifiers of the purported positive or inverse associations between coffee drinking and various human cancers. Most of these studies report no effect of genetic modifiers under investigation, while others are often conflicting with respect to the directionality of the effect.

There is *moderate* evidence regarding the association between coffee drinking and risk of colorectal adenomas. An inverse association between coffee drinking and risk of colorectal adenomas was found in several studies; however, possible uncontrolled confounding and selection biases cannot be excluded. The few studies regarding Barrett oesophagus suggest no association with coffee intake.

There is evidence that coffee drinking is associated with a beneficial effect on liver fibrosis and cirrhosis.

Impairment of glucose metabolism has been found in single-dose studies; however, both human and animal studies show that, in the longer term, coffee and caffeine may improve glucose metabolism.