Coffee and cancer

The Norwegian Women and Cancer Study / Northern Sweden Health and Disease Study

Marko Lukic

A dissertation for the degree of Philosophiae Doctor – June 2018

Coffee and cancer

The Norwegian Women and Cancer Study / Northern Sweden Health and Disease Study

Marko Lukic

A dissertation for the degree of Philosophiae Doctor (PhD)

Department of Community Medicine
Faculty of Health Sciences
UiT The Arctic University of Norway

Tromsø, Norway
2018

Acknowledgments

I would like to thank my supervisor Tonje Braaten for sharing your experience and ideas. I cannot thank you enough for meddling into my work only when I asked you to. If anyone, it was you who made me an independent researcher. As that is one of the primary goals of any PhD project – you did an outstanding job. Sorry for not finishing the simulation study. I will, promise…

Eiliv, thank you for telling me three things. First, that it was a really important finding that consuming lot of coffee does not affect the risk of cancer in Norwegian women. I did not care about p values ever since. Second, for telling me that subgroup analyses are "devil's playground". Finally, that I should not put too much effort into writing biological explanations of our findings in a discussion!

Idlir, I miss you so much, bro… That should tell you enough.

Bente, Karina, Katja, Kristin, Mie, Therese, Tor Gisle, Torkjel, I feel privileged for having you as friends and colleagues for the past for years. You made my work and life in Norway so much easier.

I would like to thank all of my co-authors, especially to Guri and Elisabete, for their contribution and insightful suggestions and inputs.

I would also like to thank my fellow PhD students. The discussions we had during my PhD were helpful, to say at least.

Women of NOWAC, thank you for participating in the study, especially those who did not answer all of the questions in the questionnaires. I would have never learned multiple imputation if it was not for you.

Finally, Aleksandra, thank you for your support in the past four years. You were there for me even at the times I have not deserved that.

Ana, this was all for you… Thank you for walking the Earth…

Love,

Marko   Tromsø, June 2018

Table of Contents

Papers 1, 2, and 3

Appendices

Summary

Background: An association between coffee consumption and the risk of cancer has long been investigated. This is particularly true for most commonly diagnosed cancer types such as, breast, endometrial, colorectal, lung, and ovarian cancer. Studies on the association between heavy coffee consumption and risk of less frequently diagnosed cancers are scarce. Coffee consumption among Scandinavian population is high, thus this is a favorable population in which to study the impact of coffee on cancer incidence.

Objectives: We aimed to quantify the association between total coffee consumption and the risk of breast, colorectal, lung, ovarian, and cancer at any site. (Paper 1) Further objective was to assess the association between filtered, boiled, and total coffee consumption and the risk of bladder, esophageal, kidney, pancreatic, and stomach cancer. (Paper 2) Finally, we aimed to summarize the existing evidence on association between coffee consumption and the risk of endometrial cancer. (Paper 3)

Methods: In paper 1**,** baseline information on total coffee consumption was collected from 91 767 women in the Norwegian Women and Cancer Study. These information was updated from the follow-up survey conducted 6-8 years after baseline. In paper 2, we used data from the Norwegian Women and Cancer Study and the Northern Sweden Health and Disease Study. Information on coffee consumption was available for 193 439 participants. Data on cancer incidence were obtained through linkage to the Norwegian Cancer Registry and the regional branch of the Swedish Cancer Registry. We used multivariable Cox proportional hazards models to calculate hazard ratios (HR) with 95% confidence intervals (CI) for the investigated cancer sites by category of total, filtered, and boiled coffee consumption. In paper 3, we searched online databases for studies published up to August 2016 that aimed to investigate the association between coffee consumption and the risk of endometrial cancer. We estimated summary relative risks (RR) for cohort studies and odds ratios (OR) for case-control studies with 95% CI by applying random effects meta-analyses. Dose-response analyses were conducted by using generalized least square trend estimation.

Results: We found and a 9% reduced risk of cancer at any site (95% CI 3%-14%, p_{trend}=0.03) in women who drank more than 3 and up to 7 cups/day, compared to women who drank ≤1 cups/day. Consumption of more than 3 and up to 7 cups/day was associated with 17% reduced risk of colorectal cancer (95% CI 2%-30%) with no evidence of linear relationship (p_{trend}=0.10). A significantly increased risk of lung cancer observed with a coffee consumption of >7 cups/day (HR=2.01, 95%CI 1.47-2.75, p_{trend}<0.001) was most likely caused by residual confounding due to smoking, as no statistically significant association was observed in never smokers (>5 cups/day HR=1.42, 95%CI

0.44-4.57, p_{trend}=0.30). No significant association was found between coffee consumption and the risk of breast or ovarian cancer.

Heavy filtered coffee consumption (≥4 cups/day) was associated with a reduced risk of pancreatic cancer (HR=0.74, 95% CI 0.57-0.95, p_{trend}=0.01). We did not observe significant associations between total and filtered coffee consumption and the risk of bladder, esophageal, kidney, and stomach cancer sites. We found some indications of a positive association between moderate boiled coffee consumption and the bladder cancer risk in women (HR=1.58, 95% CI 1.03-2.05), but this finding was not supported by the results from corresponding dose-response analysis (p_{trend}=0.56). However, we found an increased risk of bladder cancer among never smokers who were heavy filtered or total coffee consumers, and an increased risk of stomach cancer in never smokers who were heavy boiled coffee consumers.

We identified twelve prospective cohort studies and eight case-control studies eligible for inclusion in the meta-analysis of coffee consumption and endometrial cancer risk. The summary RR for highest compared with lowest coffee intake was 0.73 (95% CI: 0.67–0.80, I^2 = 36.7%) in the combined analysis of cohort and case-control studies. The corresponding RR among cohort studies was 0.76 (95% CI: 0.69–0.83, I^2 = 40.5%), and the meta-OR of 0.63 (95% CI: 0.53–0.76, I^2 = 0%) was found after pooling the results from case-control studies. One-cup of coffee increment per day was associated with 3% (95% CI: 2% -4%) lower risk of endometrial cancer in cohort studies and 12% (95% CI: 5% -18%) in case-control studies. After pooling the results from five cohort studies, the association remained significant only in women with body mass index over 30.

Conclusion: Increase in total coffee consumption was found to modestly reduce risk of cancer at any site, whereas increased filtered coffee consumption was associated with lower risk of pancreatic cancer. Our data suggest that increased coffee consumption does not affect the risk of breast, esophageal, colorectal, kidney, lung, and ovarian cancer sites. The positive associations between coffee consumption and the risk of bladder and stomach cancer were found in never smokers. The results from the meta-analysis indicate a protective effect of coffee consumption on the risk of endometrial cancer, particularly in women with obesity.

Sammendrag

Bakgrunn: En rekke studier har undersøkt sammenhengen mellom kaffeinntak og risiko for kreft, spesielt for de hyppigst forekommende kreftformene som bryst-, livmor-, tarm-, lunge- og eggstokkreft. Derimot fins det få studier av kaffeinntak og risiko for sjeldnere kreftformer. Kaffeinntaket i den skandinaviske befolkningen er høyt, og dette er et fortrinn når man ønsker å studere betydningen av kaffeinntak for kreftrisiko.

Formål: Målet var å estimere sammenhengen mellom totalt kaffeinntak og risiko for kreft i bryst, tarm, lunge og eggstokk, samt total kreft. (Artikkel 1) Videre ønsket vi å studere betydningen av tilberedningsmetode (filterkaffe og kokekaffe i tillegg til totalt kaffeinntak) for kreft i blære, spiserør, nyre, bukspyttkjertel og mage. (Artikkel 2) Til slutt hadde vi som formål å oppsummere eksisterende studier av kaffeinntak og risiko for livmorkreft. (Artikkel 3)

Metoder: I artikkel 1 ble informasjon om totalt kaffeinntak innhentet fra 91 767 kvinner i den norske studien Kvinner og kreft. Denne informasjonen ble oppdatert via et nytt spørreskjema 6-8 år senere. I artikkel 2 brukte vi data fra Kvinner og kreft og den nord-svenske helse- og sykdomsstudien NSHDS, hvor informasjon om kaffeinntak var tilgjengelig for 193 439 deltakere. Informasjon om kreftinsidens ble skaffet ved hjelp av koblinger til Kreftregisteret i Norge og det regionale kreftregisteret i Sverige. Vi brukte multivariable Cox' regresjonsmodeller for proporsjonale hasarder for å beregne hasardratio (HR) med 95% konfidensintervall (KI) for de inkluderte kreftformene ved inntak av total-, filter- og kokekaffe. I artikkel 3 søkte vi i nettbaserte databaser etter studier publisert frem til august 2016, hvor formålet var å undersøke sammenhengen mellom kaffekonsum og risiko for livmorkreft. Vi estimerte samlet relativ risiko (RR) for kohortstudier og oddsratio (OR) for kasus-kontrollstudier med 95% KI ved å anvende randomiserte meta-analyser. Dose-responseffekter ble estimert ved en «generaliserte minste kvadrat» trendanalyse.

Resultater: Vi fant en 9% redusert risiko for kreft totalt (95% KI 3% -14%, p-verdi for trend = 0,03) hos kvinner som drakk mer enn 3 og opptil 7 kopper per dag, sammenlignet med kvinner som drakk 1 kopp eller mindre per dag. Inntak av mer enn 3 og opptil 7 kopper per dag var assosiert med 17% redusert risiko for tarmkreft (95% KI 2% -30%) uten noen lineær trend (p = 0,10). Vi observerte en signifikant økt risiko for lungekreft ved kaffeinntak på mer enn 7 kopper per dag (HR = 2,01, 95% KI 1,47-2,75, p for trend <0,001), som mest sannsynlig var forårsaket av restkonfundering fra røyking, da ingen statistisk signifikant sammenheng ble observert hos aldri-røykere (> 5 kopper / dag HR = 1,42, 95% KI 0,44-4,57, p for trend = 0,30). Ingen signifikant assosiasjon ble funnet mellom kaffeinntak og risiko for bryst- eller eggstokkreft.

Høyt inntak av filterkaffe (≥ 4 kopper / dag) var assosiert med redusert risiko for kreft i bukspyttkjertelen (HR = 0,74, 95% KI 0,57-0,95, p for trend = 0,01). Vi observerte ingen signifikante sammenhenger mellom inntak av total-, filter- eller kokekaffe og risikoen for kreft i blære, spiserør, nyre eller mage. Vi fant indikasjoner på en positiv sammenheng mellom moderat inntak av kokekaffe og blærekreft hos kvinner (HR=1.58, 95% KI 1.03-2.05), men dette funnet støttes ikke av resultatene fra dose-responsanalysen. (p for trend = 0.56). Imidlertid fant vi en økt risiko for blærekreft blant røykere med høyt inntak av filterkaffe eller kaffe totalt, og en økt risiko for magekreft hos aldri-røykere med høyt inntak av kokekaffe.

Vi identifiserte tolv prospektive kohortstudier og åtte kasus-kontrollstudier som var kvalifisert for inkludering i meta-analysen av kaffeinntak og risiko for livmorkreft. Samlet RR for høyeste sammenlignet med laveste kaffeinntak var 0,73 (95% KI: 0,67-0,80, I2 = 36,7%) i den kombinerte analysen av kohort- og kasus-kontrollstudier. Tilsvarende RR blant kohortstudier var 0,76 (95% KI: 0,69-0,83, I2 = 40,5%), og meta-OR 0,63 (95% KI: 0,53-0,76, I2 = 0%) ble funnet etter å ha samlet resultatene fra kasus-kontrollstudier. En kopp økning i kaffeinntak per dag var assosiert med 3% (95% KI: 2% -4%) lavere risiko for livmorkreft i kohortstudier og 12% (95% KI: 5% -18%) i kasus-kontrollstudier. Etter å ha samlet resultatene fra fem kohortstudier, forble sammenhengen signifikant bare hos kvinner med kroppsmasseindeks over 30.

Konklusjoner: Vi fant en moderat reduksjon i risiko for kreft totalt ved høyt inntak av kaffe, mens økt inntak av filterkaffe var forbundet med lavere risiko for kreft i bukspyttkjertelen. Våre data tyder på at økt kaffeinntak ikke påvirker risikoen for kreft i bryst, spiserør, tarm, nyre, lunge eller eggstokker. En positiv assosiasjon mellom kaffeinntak og risiko for blære- og magekreft ble funnet bare hos røykere. Resultatene fra meta-analysen indikerer en beskyttende effekt av kaffeinntak på risikoen for livmorkreft hos kvinner med fedme.

List of papers

This thesis is based on the following papers, hereafter referred in the text as Papers 1,2, and 3.

PAPER 1

Lukic M, Licaj I, Lund E, Skeie G, Weiderpass E, Braaten T. **Coffee consumption and the risk of cancer in the Norwegian Women and Cancer (NOWAC) Study.** Eur J Epidemiol. 2016;31(9):905-16.

PAPER 2

Lukic M, Nilsson LM, Skeie G, Lindahl B, Braaten T. **Coffee consumption and risk of rare cancers in Scandinavian countries.** Eur J Epidemiol. 2018;33(3):287-302.

PAPER 3

Lukic M, Guha N, Licaj I, van den Brandt PA, Stayner LT, Tavani A, et al. **Coffee Drinking and the Risk of Endometrial Cancer: An Updated Meta-Analysis of Observational Studies.** Nutr Cancer. 2018;70(4):513-28.

Abbreviations

CYP	Cytochrome P450
NAT2	N- acetyltransferase 2
IARC	International Agency for Research on Cancer
OR	Odds Ratio
CI	Confidence Interval
WCRF	World Cancer Research Fund
EPIC	European Prospective Investigation into Cancer and Nutrition
NOWAC	Norwegian Women and Cancer Study
NSHDS	Northern Sweden Health and Disease Study
VIP	Västerbotten Intervention Programme
MONICA	Monitoring Trends and Determinants in Cardiovascular Disease
NSDD	Northern Sweden Diet Database
BMI	Body mass index
HR	Hazard ratio
RR	Risk ratio
FFQ	Food-frequency questionnaires
MCAR	Missing completely at random
MAR	Missing at random
MNAR	Missing not at random
MICE	Multiple imputation by chained equations
CPU	Central processing unit
PH	Proportional hazards
DNA	Deoxyribonucleic acid

1 Introduction

1.1 Coffee

1.1.1 Biological classification and history

The genus of plants known as *Coffea* consists of over 70 species (1, 2). Most of the *Coffea* species can be found in the Equatorial region with the optimum altitude for growth being between 1300 meters and 1600 meters (3, 4). Our morning coffee is most likely made either of *Coffea arabica* or *Coffea canephora (s. Coffea robusta),* the two species dominating the coffee industry as they account for approximately 60% and 40% of the world coffee consumption, respectively. Other less grown species include *Coffea liberica* and *Coffea excelsa*, which contribute to up to 2% of world's gross production and are considered to be of poorer overall quality (1, 2, 5).

It is believed that coffee consumption originates either from Ethiopia or Yemen (6). The modern way of processing coffee beans by roasting and grounding was reported first in the Yemeni city Mocca in early 15th century (7). Even though the Ottoman Turks who had ruled Yemen tried to confine coffee use strictly within its borders, coffee consumption has spread via Istanbul to Venice in the beginning of the 17th century. Some decades later, coffee appeared first in France, and later in Vienna and England, reaching North America presumably in 1668 (6, 7).

The first mention of coffee in Norway was recorded in 1694. During the early 18th century, coffee supressed alcoholic beverages as a "social lubricant" among the upper class of Norwegian society (8). By the late 18th century, approximately 250-300 gr of unroasted coffee per person was imported to Norway yearly through Copenhagen (8). The amount increased ten-fold by the mid-19th century when, Friele, a merchant from Bergen, started trading salted cod with coffee producers in Brazil, importing over 900 tonnes of coffee per year (9). At the time, coffee was made in copper kettles by boiling, with fish-skin and/or hot charcoal being commonly added into kettles before serving (10). Due to an increased coffee consumption among Norwegians throughout 1850s and 1860s, health authorities rose their concerns about its health effects for the first time (11).

By the end of the 19th century, yearly coffee consumption in Norway had reached almost 4 kg per capita. This figure has fluctuated during the 20th century, rising up to 6.5 kg per person during the prohibition between 1916 and 1927, and plummeting to only 50 grams per week during the German occupation of Norway (12). After the World War 2, coffee consumption in Norway increased again, with 50% of coffee nowadays being imported from Brazil, and 25% from Colombia and Guatemala (12). Between 1997 and 2011, average consumption of coffee in Norway reached 9.4 kg/year per capita, and only Finland among Nordic countries was ahead with 11.7 kg (13). In the past few

decades, the preferred brewing method has changed among Norwegians. Filtered coffee is now considered by far the most popular brewing method surpassing both boiled and instant coffee as the alternatives (14). As from the late 1990's and throughout 2000's other types of coffee drinks such as macchiato, espresso, cappuccino, or café latte has become increasingly popular, while the consumption of decaffeinated coffee in Norway remains uncommon to this day (15).

In Sweden, the average roasted coffee consumption between 2006 and 2016 was stable and averaged 7.95 kilograms per capita, which is a slight decrease compared to the period between 1997 and 2005 (8.2 kilogram per capita) (13, 16). The consumption peaked at 2010 reaching 8.8 kilogram per person. However, the following year, the consumption of only 7.3 kilogram of roasted coffee was reported per capita. The data from 2016 have shown the consumption of roasted coffee in Sweden amounted to 8.1 kilograms per capita. The total annual volume of roasted coffee consumed in Sweden averages 80 thousand metric tons (16).

1.1.2 Coffee constituents

Coffee as a beverage consists of numerous components which concentration and bioavailability depend on coffee type, roasting and brewing methods (17).

Caffeine

Caffeine is an alkaloid also known as 1,3,7-trimethylxanthine, with a chemical formula $C_8H_{10}N_4O_2$ (Figure 1) (18). It is considered the most frequently consumed behaviorally active substance in the world (17-19), and other than in coffee, it can be found in tea, cocoa beverages, chocolate, energy drinks, and pre-workout beverages. On average, *Coffea robusta* contains more caffeine compared to *Coffea arabica* (19-21 mg/g vs. 10-12 mg/g, respectively) (20, 21). The content of caffeine seems to be dependent on brewing method, with boiled coffee having higher caffeine concentration per 100 ml compared to filtered coffee (22).
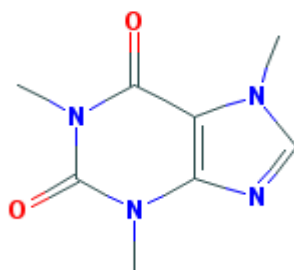

Figure 1: Chemical structure of caffeine. Reprinted from: National Center for Biotechnology Information. PubChem Compound Database Copyright © 2018 with open access (23).

The peak plasma concentration of caffeine is reached 15-20 minutes after oral ingestion. It is absorbed completely by the stomach and small intestine, and it is able to pass all biological membranes (24, 25). The primary metabolism of caffeine in liver involves CYP1A2 (Cytochrome P450 1A2) enzyme that belongs to a cytochrome P450 oxidase enzyme system, and by N-acetyltransferase 2 enzyme (NAT2) (25-30). Caffeine has a half-life of approximately 5 hours in healthy adults and is mainly metabolized to paraxanthine (70-80%), and only a small fraction is excreted unchanged in the urine (25, 31).

Caffeine exhibits the ability to improve physical (25, 32) and cognitive performance, such as vigilance and decreased reaction times (25). It is also shown to manage the symptoms of Parkinson's disease (33, 34) and to have antioxidant properties (35, 36). Adverse effects of caffeine, such as increase of anxiety or jitteriness, are mainly the result of excessive amount of caffeine consumed and can also be a consequence of caffeine withdrawal (37, 38).

Diterpenes

Two diterpenes found in a coffee bean are cafestol and kahweol which were found to have anticarcinogenic properties (39, 40) (Figure 2). Studies have shown that kahweol could induce apoptosis in human leukemia cells (41), to reduce gentoxicity in hepatoma cells (42), and to induce synthesis of endogenous antioxidants (43), whereas both cafestol and kahweol were reported to induce apoptosis in human malignant pleural mesothelioma (44). On the other hand, coffee diterpenes were also found to increase serum cholesterol and might cause extracellular accumulation of low-density lipoproteins (45-48). Filtered coffee, as one of the methods of preparing coffee beverage, was found to have lower levels of diterpenes compared to boiled, espresso, or French press coffee (49-51), as the paper filter manages to block the passage of fine particles into the brew, and diterpenes being retained by the spent coffee (52, 53).
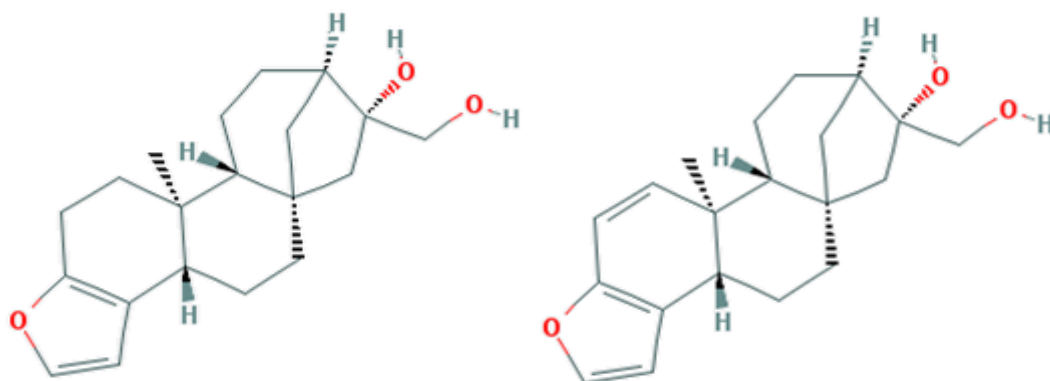

Figure 2: Chemical structure of cafestol and kahweol. Reprinted from: National Center for Biotechnology Information. PubChem Compound Database Copyright © 2018 with open access (54, 55).

Chlorogenic acids

Chlorogenic acids are polyphenolic compounds, with 5-caffeoylquinic acid being its major component found in coffee, and neochlorogenic, cryptochlorogenic, feruloylquinic, and dicaffeoylquinic acids also present in large quantities (18, 56-58) (Figure 3). It is one of the coffee ingredients with very high antioxidant activity (57, 59-63). In addition, it has been speculated that chlorogenic acids could decrease the risk of some cancers, and the proposed mechanism is that it reduces glucose levels in the blood and increases insulin sensitivity (64-67). Concentration of chlorogenic acids in a regular cup of coffee depends on type of coffee bean, roasting temperature, and brewing method (22, 57, 58, 68-70). *Caffea robusta* was found to have a higher content of chlorogenic acid compared to *Caffea arabica,* and therefore the higher antioxidant activity (22, 57, 61). Similarly, more pronounced antioxidant activity of boiled compared to filtered coffee could be the result of higher concentrations per cup of not only diterpenes but chlorogenic acids as well (22).
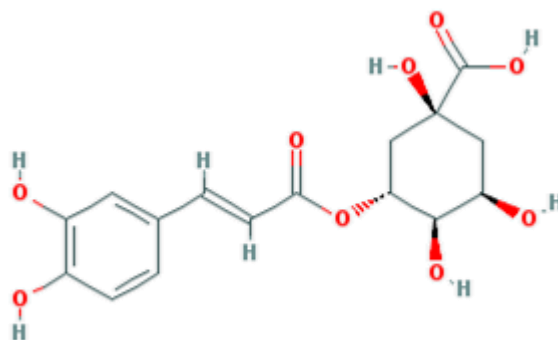
Figure 3: Chemical structure of chlorogenic acid. Reprinted from: National Center for Biotechnology Information. PubChem Compound Database Copyright © 2018 with open access (71).

Coffee Maillard Reaction Products

During the process of high temperature roasting of green coffee beans, high molecular weight, polymeric chemicals named melanoidins are created as products of Maillard reaction (21, 72). The structures of these chemicals responsible for the taste and aroma of coffee beverage are difficult to determine, as melanoidins are modified to less known structures from polysaccharides, proteins, and phenolics (21, 73, 74). The products of Maillard reactions were also shown to have antioxidant properties (72, 75, 76), and the mechanism of antioxidant activity includes scavenging hydroxyl and proxy radicals, and breaking the radical chain (77). *In vivo*, these molecules were found to have a protective effect against oxidative stress in human hepatoma cells (78), to increase survival of human neuroblastoma cells from oxidative damage (75), and to suppress liver oxidative stress in rats (79).

1.1.3 Cancer incidence in Norway

The incidence rate for all cancer sites combined has increased by 4.4% among Norwegian women in the five-year period from 2012 to 2016 compared to the period between 2007 and 2011. Breast, colorectal, and lung cancer remain the three most frequently diagnosed cancers in Norway and worldwide (80, 81). In Norway, age-standardized incident rate of breast cancer per 100 000 person-years has increased by 7% from 2007–11 to 2012–16. Comparing the same periods, the incidence rate of lung cancer has increased by 9.4%. Women in Norway have one of the highest incidences of colorectal cancer in the Nordic countries, with 1588 new cases of colon and 517 new cases of rectal cancer diagnosed in 2016. The incidence of colon cancer has increased almost three-fold between 1955 and 2014, while rectal cancer rates have stabilized after 1990s. On the other hand, a reduction in rates was recorded for ovarian (-7.4% between 2007–11 and 2012–16) and endometrial cancer (-5.9%). In 2016, age-standardized (Norwegian standard) incident rate of esophageal cancer was 2.4 per 100 000 women compared to 8.5 per 100 000 men. Similarly, higher rates are observed in Norwegian men compared to women for stomach (12.1 per 100 000 vs. 5.0 per 100 000), pancreatic (15.3 per 100 000 vs. 11.5 per 100 000), kidney (22.9 per 100 000 vs. 10.1 per 100 000), and urinary tract (52.8 per 100 000 vs. 16.9 per 100 000) cancer sites (80).

1.1.4 Cancer incidence in Sweden

From 2007 to 2016, the breast cancer incidence rates in Sweden have increased from 144 per 100 000 to 163.4 per 100 000 women, and breast cancer remained the most frequently diagnosed cancer among Swedish women. In Swedish men, prostate cancer is the most commonly diagnosed cancer with about 10,500 new cases being diagnosed in 2016. In the same year, the incidence rate of lung cancer was similar in men (35.5 per 100 000) and women (35.9 per 100 000) whereas higher rates of colon cancer were reported in men (47.1 per 100 000 vs. 42.1 per 100 000). Cancer of upper digestive tract was also more common in men (19.8 per 100 000) compared to women (9.6 per 100 000), which was also true for cancer of liver, pancreas and hepatobiliary tract (25.9 per 100 000 vs. 19.6 per 100 000), and cancer of kidney and urinary tract (62.2 per 100 000 vs. 23.5 per 100 000) (82).

1.2 Coffee consumption and the risk of cancer – the story so far

Because of the vast popularity of coffee beverages worldwide, any causal association between coffee consumption and chronic diseases would have a significant public health impact. The amount of evidence from epidemiological/health effect studies which had the aim to explore the association between coffee consumption and the risk of cancer, was mounting in the past two decades. In 2016,

the International Agency for Research on Cancer (IARC) published the Monograph in which they have evaluated the carcinogenicity of drinking coffee, maté, and very hot beverages, based on the available literature. In a summary of the final evaluations, the authors of the monograph stated that coffee drinking was not classifiable according to its carcinogenicity in humans (Group 3): "there was inadequate evidence of carcinogenicity in experimental animals and evidence suggesting lack of carcinogenicity in humans for cancers of the pancreas, female breast, and prostate, liver, and uterine endometrium, with inverse associations noted for the latter two sites" (83).

Coffee consumption and bladder cancer

The two epidemiological studies from Norway that aimed to explore the association between coffee drinking and the risk of bladder cancer included 16 555 and 43 000 Norwegian men and women, respectively (84, 85). The authors of both studies did not observe increase in the bladder cancer incidence among heavy coffee consumers. The recent meta-analysis of 25 case-control and five cohort studies revealed an overall meta-odds ratio (OR) of 1.33 (95% confidence interval (CI) 1.19-1.48) between coffee consumption and the bladder cancer risk (86). Finally, in the 2016 Monograph, the authors concluded there was no consistent evidence of an association between coffee consumption and bladder cancer risk, and that positive associations observed in some studies are most likely due to inadequate adjustment for smoking exposure, a known risk factor (83).

Coffee consumption and breast cancer

The two most recent meta-analyses on coffee consumption and the risk of breast cancer were published in 2013 and included 37 (87) and 26 (88) observational studies. Jiang et al. reported an inverse association for postmenopausal women and women that were BRCA1 mutation carriers (87), whereas Li et al. concluded that coffee drinking was not associated with the breast cancer risk (88). In Norway, Stensvold and Jacobsen found a statistically non-significant positive association between coffee consumption and the risk of most frequently diagnosed cancer in Norway (85). As mentioned above, the authors of IARC's Monograph concluded that evidence from the available studies indicate lack of carcinogenicity for the female breast (83). The World Cancer Research Fund (WCRF) in their Continuous Update Project on how diet, nutrition, physical activity and body weight affect cancer risk and survival, concluded that the evidence on coffee and breast cancer risk are limited (89).

Coffee consumption and colorectal cancer

In the recent meta-analysis, Gun et al. found a 7% decreased risk of colon cancer for an increase in coffee intake by 4 cups per day (95% CI 1%-12%). In conclusion, the authors have stated that coffee consumption of at least 5 cups of coffee per day was inversely associated with the risk of colorectal cancer (90). Similarly, the findings from the Monograph suggest that that there are moderate evidence

of protective effect of coffee drinking on the risk of colorectal adenoma (83), whereas the authors of WCRF's Continuous Update Project conclude that the evidence are limited/inconclusive (91). Among Norwegian women, the reported inverse association was not statistically significant for either colon or rectal cancer sites (85).

Coffee consumption and endometrial cancer

In two most recently published meta-analyses, coffee consumption was found to be inversely associated with the risk of endometrial cancer, and that the observed effect may be modified by body mass index (BMI), previous use of hormone replacement therapy (92), and menopausal status (93). The overall conclusion from these meta-analyses are in line with the conclusion from IARC's Monograph (83), and from the Continuous Update Project (94).

Coffee consumption and esophageal cancer

There are little evidence indicating that coffee is associated with esophageal cancer (95, 96). However, there are strong evidence that consumption of hot beverages increases the risk of esophageal cancer (83, 96), based on the findings from one meta-analysis (95) and two studies from South America (97, 98).

Coffee consumption and lung cancer

The results from a 2016 meta-analysis of 17 observational studies suggested that coffee consumption is associated with an increased risk of lung cancer (99), which was previously found in the study by Stensvold and Jacobsen (85). Galarraga et al. speculated that this association would be non-existent if effect of smoking is properly accounted for in the analyses, and indicated the importance of pooled analyses with large study groups of never smokers (100). In the WCRF's Continuous Update Project report, the authors concluded that the evidence on coffee and lung cancer incidence are limited/inconclusive (101).

Coffee consumption and ovarian cancer

No association between coffee intake and incident ovarian cancer is was found in the study from the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort, and from a meta-analysis by the same authors (102). The same conclusion was made in the umbrella review of meta-analyses of coffee consumption and multiple health outcomes (103), and from the results of the Continuous Update Project (104).

Coffee consumption and pancreatic cancer

A 2012 meta-analysis revealed no apparent association between high coffee intake and the risk of pancreatic cancer (105). However, in more recent meta-analysis of 20 cohort studies, Ran et al. concluded that high coffee consumption was in fact associated with the decreased pancreatic cancer risk (106). This finding was not supported by the IARC's 2016 Monograph, nor by the authors of the Continuous Update Project (83, 107). Similarly, no significant relationship was found in two studies from Norway (84, 85).

Coffee consumption and renal cancer

In the Norwegian study from 1986, Jacobsen et al. found a strong inverse association between coffee intake and the renal cancer risk (84). This finding was later refuted by Stensvold and Jacobsen, who found no such relationship based on the data from 43 000 Norwegian men and women (85). This later finding was also backed up by the conclusion from the Continuous Update Project (108).

Coffee consumption and stomach cancer

Five meta-analyses published in 2015 and 2016 reported conflicting results regarding the relationship between coffee intake and the incident stomach cancer, ranging from decreased risk (109), no association for stomach cancer risk overall (110) and in the population outside of United States (111, 112), to an increased risk (113). Limited evidence of an association was reported by the Continuous Update Project (114), which was also found previously in the two studies from Norway (84, 85).

2 Aims

The overall aim of the thesis is to explore the association between coffee consumption and the risk of cancer.

PAPER 1

The aim was to investigate the relationship between heavy coffee consumption and the risk of breast, colorectal, ovarian, and lung cancers, as well as cancer at any site (overall cancer risk), in the Norwegian Women and Cancer (NOWAC) study.

PAPER 2

By pooling the data from two Nordic cohorts: the Norwegian Women and Cancer (NOWAC) Study and the Northern Sweden Health and Disease Study (NSHDS), we explored the association between filtered, boiled, and total coffee consumption and the risk of bladder, esophageal, kidney, pancreatic, and stomach cancer.

PAPER 3

We aimed to summarize the available evidence on the association between coffee intake and endometrial cancer risk by conducting an updated dose-response meta-analysis of observational studies.

.

3 Material and methods

3.1 Papers 1 and 2

3.1.1 The Norwegian Women and Cancer Study

The NOWAC study is population based cohort study that involves approximately 172 000 women from all over Norway. It was initiated in 1991 with the primary aim to investigate risk factors for breast cancer. The NOWAC Study has been described in detail by Lund et al (115). In short, random samples of Norwegian women aged 30-70 years was drawn from the Norwegian Central Population Registry and were invited to participate. The enrolment of women was conducted in three waves (1991, 1995-1997, and 2003-2007) (Figure 4). The food frequency questionnaire (FFQ) was added during the second wave of enrolment, whereas the collection of blood samples was initiated in 2003. More than 172 000 accepted and completed a questionnaire regarding their lifestyle, diet, and health status (overall response rate: 52.7%), and the NOWAC biobank consists of over 60 000 blood samples. All the participants received two follow-up questionnaires within 5 to 8 years between each follow-up. The NOWAC Study was approved by the Regional Committee for Medical Research Ethics and the Norwegian Data Inspectorate. All women gave written informed consent.

3.1.2 Northern Sweden Health and Disease Study

The NSHDS contains survey and biobank data from about 166 000 men and women in northernmost Sweden. It was initiated in 1985 and includes three population-based sub-cohorts: the Västerbotten Intervention Programme (VIP) cohort (participants aged 30, 40, 50 or 60 years), the MONICA (Monitoring Trends and Determinants in Cardiovascular Disease) cohort (participants aged 25-74 years), and the mammography screening cohort (women aged 50-69 years). Dietary data administered by the Northern Sweden Diet Database (NSDD) are available in the VIP and MONICA cohorts. The participants of the ongoing VIP cohort that runs in the Northern Sweden's Västerbotten county have undergone extensive health examination and have also answered questionnaires regarding diet, lifestyle and health conditions. The mean participation rate has been around 60% (116).

The MONICA cohort includes inhabitants in the Västerbotten and Norrbotten counties randomly selected from the population registries that were updated every fourth to fifth year (117). The participation rate over the years of recruitment varied from 62% to 81%. The questionnaires used in the MONICA cohort are very similar to those used in the VIP cohort (116). The coffee study within the NSHDS was approved by the Regional Ethical Review Board of Northern Sweden, and all participants gave written informed consent.

Figure 4: Cohort enrollment in the NOWAC study

3.1.3 Study population

For paper 1, we used the information from the questionnaires of women enrolled in 1991-1992, 1996-1997, 2003, and 2004. These women completed baseline food frequency questionnaires in 1998, 1996-1997, 2003, and 2004, respectively. The information collected during the first wave (1991-1992) were not used in the study, as the version of questionnaires that was sent out did not include questions regarding diet. However, as the women enrolled during the first wave of data collection answered dietary questions in the follow-up survey in 1998, we used this information as baseline data for the present study. In total, 98 405 women answered the question regarding their coffee consumption.

Women with prevalent cancer other than non-melanoma skin cancer at baseline and those who emigrated or died before the start of follow-up (N=4395), those who were diagnosed with cancer after they emigrated (N=9), and those with total energy intake above 15 000 kJ or below 2500 kJ per day (N=619), and those with missing information on coffee intake at baseline (N=1615) were excluded from the study. Our final analytical study sample consisted of 91 767 women. Follow-up information were available from 79 461 of these women, who received the follow-up questionnaire before the end of the study, 6-8 years after baseline data collection. The rest of the women (N=12 306) received the baseline questionnaire in 2004, while the follow-up questionnaire was sent out to them after the study had ended.

In paper 2, the NOWAC cohort initially included 101 320 women, while the NSHDS cohort contributed 103 256 participants. As in paper 1, the data collected during 1991-1992 were not used in the study. After exclusion of those participants with prevalent cancer other than non-melanoma skin cancer at baseline, those who emigrated or died before the start of follow-up (N=8101), those that had missing information on coffee consumption (N=1615), and those with total energy intake above 15 000 kJ or below 2500 kJ/day (N=1362), the final sample consisted of 145 247 women and 48 192 men.

3.1.4 Information on coffee consumption and covariates

In the NOWAC cohort, the same question regarding coffee consumption was asked at baseline and at follow-up: "How many cups of each kind of coffee (boiled, filtered, instant) did you usually drink during the past year?" Women could choose from the following answers: never/seldom, 1-6 cups/week, 1 cup/day, 2-3 cups/day, 4-5 cups/day, 6-7 cups/day, and ≥8 cups/day for each brewing method. For paper 1, we calculated total coffee consumption by summing the frequencies of each of the brewing methods, and categorized it as ≤1 cup/day (light consumers), more than 1 up to 3 cups/day (low moderate consumers), more than 3 up to 7 cups/day (high moderate consumers), and >7 cups/day (heavy consumers).

In the NSHDS cohort, the participants were asked the number of occasions on which they consumed filtered or boiled coffee with the following alternatives: never, a few times/year, 1-3 times/month, 1 time/week, 2-3 times/week, 4-6 times/week, 1 time/day, 2-3 times/day, and >4 times/day.

For the purpose of the paper 2, we assumed that 1 time/day from the NSHDS cohort matched 1 cup/day from the NOWAC cohort. Total coffee consumption by summing the frequencies of filtered, boiled, and instant coffee in the NOWAC cohort and filtered and boiled coffee in the NSHDS cohort. Filtered, boiled, and total coffee consumption was then categorized as light consumption (≤1 cup/day), moderate consumption (>1-< 4 cups/day), and heavy consumption (≥4 cups/day).

In paper 1, the following information were collected at both baseline and follow-up: BMI (body mass index), physical activity, alcohol consumption, total energy intake, and use of hormone replacement therapy (never, former, current), smoking status (never, former, current), and number of pack-years (calculated as number of cigarettes smoked/day divided by 20 and multiplied by years of smoking). We categorized as former smokers at follow-up those women who reported they were current or former smokers at baseline and non-smokers at follow-up (N=1608).

In paper 2, we also utilized information on smoking status (never, former, current), alcohol consumption, BMI, total energy intake, and self-reported history of diabetes.

3.1.5 Cancer incidence, death, and emigration

We used the unique 11-digit personal number assigned to every legal resident in Norway, and the unique 12-digit personal number assigned to residents in Sweden to obtain information on cancer incidence, death, and emigration through linkage to the Norwegian Cancer Registry, the Cause of Death Registry, the Norwegian Central Population Register, the regional branch of the Swedish Cancer Registry, and Swedish National Cause-of-death Registry.

The 7th Revision of the International Statistical Classification of Diseases, Injuries and Causes of Death was used to classify breast (170.0-170.9), colorectal (153.0-154.0), ovarian (175.0-175.9), and lung (162.0-162.1) (paper 1), and bladder (181.0-181.9), esophageal (150.0-150.9), kidney (180.0-180.9), pancreatic (157.0-157.9), and stomach (151.0-151.9) cancer cases (paper 2) in the national and regional cancer registries.

3.1.6 Statistical analysis

In paper 1, we applied baseline information on coffee consumption and covariates until potential follow-up information, date of diagnosis of any incident cancer other than non-melanoma skin cancer, death, or emigration, whichever occurred first. Thereafter, we updated information on coffee

consumption and smoking variables until diagnosis of any incident cancer other than non-melanoma skin cancer, until death, emigration or the end of the study period (31 December 2013), whichever occurred first. In paper 2, person-years were calculated from start of follow-up until diagnosis of any incident cancer other than non-melanoma skin cancer, death, emigration, or the end of the study period (31 December 2014), whichever occurred first.

Cox proportional hazards regression models were used to calculate hazard ratios (HRs) for developing breast, colorectal, ovarian, or lung cancer, as well as cancer at any site other than non-melanoma skin cancer in paper 1, and bladder, esophageal, kidney, pancreatic, or stomach cancer in paper 2, with 95% CIs for each coffee consumption group. Light consumers (i.e., those drinking ≤1 cup/day), were used as the reference group, and attained age was used as the underlying time scale in both papers. In paper 1, all models were stratified by questionnaire subcohorts, (i.e. during which of the three waves of data collection a participant was included in the cohort), and by study cohort (NOWAC/NSHDS) in paper 2.

In paper 1, analyses for each cancer site were adjusted for known risk factors for specific cancer type in the preliminary, complete-case analysis: menopausal status (premenopausal/postmenopausal), smoking status (never, former, current), age at smoking initiation (<20, ≥20 years), number of pack-years (≤14, 15-19, ≥20), exposure to cigarette smoke during childhood (yes/no), duration of education (≤9, 10-12, 13-16, ≥17 years), body mass index (BMI, ≤18.49, 18.5-24.9, 25-29.9, and ≥30 kg/m^2), physical activity level (1-4, 5-6, 7-10), alcohol consumption (0, 0.1-3.99, 4-9.99, ≥10 g/day), number of children (0, 1-2, ≥3), age at first birth (<20, 20-24, 25-29, ≥30 years), ever use of oral contraceptives (yes/no), duration of oral contraceptive use in years (continuous), use of hormone replacement therapy (never, former, current), maternal history of breast cancer (yes/no), total energy intake (tertiles, kJ/day), intake of fibers (<=20, >20 g/day), intake of processed meat (continuous, g/day), intake of red meat (<=10, 10.01-20, >20, g/day), height (continuous, cm), and participation in mammography screening (yes/no). For the analyses of colorectal, lung, and cancer at any site, smoking exposure was modelled as five-categories variables, which included the information on smoking status, age at smoking initiation, and number of pack-years. We built the final models by assessing if the removal of the covariate lead to a change in the regression coefficients of at least 10% in any of the coffee consumption groups. In paper 2, we adjusted for a variety of *a priori* selected risk factors: sex, smoking status (never, former, current), BMI (≤18.49, 18.5-24.9, 25-29.9, and ≥30 kg/m^2), alcohol consumption (0, 0.1-3.99, 4-9.99, ≥10 g/day), and self-reported history of diabetes (yes/no). In addition, the analyses of filtered coffee were adjusted for boiled coffee consumption and vice-versa.

The proportional hazards assumption was assessed by testing an interaction between coffee consumption and the logarithmic transformation of participants' age in paper 1, and by assessing Schoenfeld residuals in paper 2. In both papers, we tested for linear trend across coffee consumption categories by assigning a median value to each category of the ordinal coffee consumption variable, which was then modeled as a continuous variable in the analysis.

We checked if smoking status, BMI, and physical activity level modified the effect of total coffee consumption on studied outcomes in paper 1, and if BMI was effect modifier in the analyses of each brewing type in paper 2. In paper 1, by using information on women that were never smokers during the entire study period, we conducted the analyses of lung cancer to deal with residual confounding due to smoking. In paper 2, we conducted subgroup analyses according to smoking status (never/ever) for all of the outcomes.

In paper 2, to assess a possible non-linear relationship between coffee consumption and the study outcomes, we modeled restricted cubic splines with four knots, with its locations based on Harrell's recommended percentiles of the total and filtered coffee consumption (118), and positioned at the 25th, 60th, and 95th percentiles of the boiled coffee distribution. We used a Wald-type test to assess if the coefficients of the second and third spline in filtered and total coffee analyses, and if the second spline's coefficient in boiled coffee analyses were equal to zero.

The use of repeated measurement in paper 1 on coffee consumption allowed us to conduct an extensive lag analysis in order to check for possible reverse causality. First, we have performed the analyses for every outcome after excluding cancers at the corresponding sites diagnosed during the first two years of follow-up. Second, we had excluded cancer cases diagnosed during the first year of follow-up while also censoring at the time of answering the second questionnaire those cancer cases diagnosed during the first year after they received the second questionnaire. In paper 2, a possible reverse causality was assessed by excluding cancer cases of interest diagnosed during the first year of follow-up.

3.1.7 Multiple imputation

In paper 1, assuming that data was missing at random, we performed multiple imputation by chained equations to deal with missing data. Twenty imputed datasets were created with ten iterations per dataset, in order to reduce sampling variability from the imputation simulation (119). The missing values were then replaced by imputed values based on the observed information. We created imputation models for each outcome, including all of the variables from the final analysis of the specific cancer sites, and the set of variables that we assumed could increase the predictive power of the imputation procedure, regardless of whether the variable(s) were used in the multivariable Cox regression model. Any significant interaction term between coffee intake and smoking status, BMI or

physical activity level in addition to the outcome indicator, and the Nelson-Aalen cumulative hazard estimator were included as predictors in all the imputation models (120). We used predictive mean matching using the 100 closest individual observations (nearest neighbors) from which imputed values were drawn as well as logistic regression, ordinal logistic regression, and multinominal logistic regression to impute continuous, binary, ordinal, and nominal variables, respectively.

The estimates from the twenty imputed datasets were combined using Rubin's rules in order to obtain HRs and corresponding 95% CIs (121, 122).

In our study, the single population parameter of interest was a log HR from a Cox regression model, which will be denoted as Q. Then the multiple imputation point estimate of Q is the average of the m complete-data estimates (123):

$$\overline{Q} = \frac{1}{m} \sum_{t=1}^{m} \widehat{Q}^{(t)}$$

Further, we estimated a within-imputation variance component as the average of the complete-data variance estimates (123):

$$W = \frac{1}{m} \sum_{t=1}^{m} U^{(t)}$$

Between-imputation variance is calculated by a combination of the complete-data point estimates (123):

$$B = \frac{1}{m-1} \sum_{t=1}^{m} (\widehat{Q}^{(t)} - \overline{Q})^2$$

Finally, the total variance is calculated as:

$$T = W + \left(1 + \frac{1}{m}\right) B$$

3.2 Paper 3

3.2.1 Search strategy, study selection, and data extraction

We performed a search of the electronic databases PubMed and Embase for studies published until August 2016 with the aim to quantify association between coffee intake and the risk of endometrial cancer. The following search strategy has been applied: *("coffee"[MeSH Terms] OR coffee[Text Word]) AND ("Endometrium"[Mesh] OR endometrial OR endometrium OR uterus OR corpus uteri) AND "Neoplasms"[Mesh] OR neoplasms OR cancer OR carcinogenic OR tumor) AND ("Epidemiology"[Mesh] OR "Epidemiologic Studies"[Mesh] OR "Cohort studies"[Mesh] OR "Case-control studies"[Mesh] OR case-referent OR case-control OR cohort)*. We included case-control, retrospective or prospective cohort studies that reported effect estimates with corresponding 95% CI for the association. We excluded the studies that did not adjust for body mass index and smoking as these are considered as key confounders.

The data were independently extracted by two authors, and any disagreements were resolved by mutual discussion. The following information were extracted from each included study: first author's last name, publication year, country of origin, study design, age of participants at study initiation, number of participants, person-years, and endometrial cancer cases, mean, median or duration of follow-up (cohort studies), number and type of cases and controls, mean age of cases and controls (case-control studies), covariates adjusted for in the analyses, information on principal strengths and limitations, risk ratios (RRs) from cohort studies and ORs from case–control studies with 95% CIs for each coffee consumption category.

3.2.2 Statistical analysis

ORs from case-control study and RRs from cohort studies were log transformed, after which standard errors of log-transformed effect estimates were calculated to compute summary RR or OR with 95% CI for the highest vs lowest (reference) category of coffee intake using random-effect models. The weight of each study was inversely proportional to the within-study sampling variances (124). We also conducted alternative analyses in which we first combined category specific estimates among coffee drinkers within each study into a single estimate for moderate to heavy coffee drinkers' using a fixed effect model, after which we pooled single estimates using a random-effects model.

We performed subgroup analyses according to BMI (<25, 25-30, >30), smoking status (never, former, current) use of hormonal replacement therapy (never, ever), caffeination status (caffeinated, decaffeinated), study location (Europe, North America), postmenopausal status for cohort studies, and the type of controls (hospital-based, population-based), postmenopausal status, and study location (Europe, Asia, North America), for case-control studies.

A dose-response analysis was conducted using generalized least squares for trend estimation method (125, 126). First, as the dosage values, we used medians reported in the studies or estimated them if the information was not available. Then, a variance-covariance matrix of the beta coefficients (log transformed RRs/ORs) in each of the studies was estimated to obtain dose-response relationship curves (125, 127).

We modeled restricted cubic splines with three knots positioned at 2%, 25%, and 80% percentile of the coffee consumption distribution for cohort studies, and at 5%, 45%, and 80% percentile of the distribution for case-control studies. A non-linear relationship was assessed by testing the null hypothesis that the coefficients of the second spline were equal to zero (128).

In addition to a chi-square test, the heterogeneity between the studies was quantified by I^2 statistic:

$$I^2 = \left(\frac{Q - \mathrm{df}}{Q}\right) x \ 100\%$$

where Q represents the value of chi squared statistics, i.e. the test that assesses if the observed differences in individual study results are compatible with chance alone, and df represents the tests degrees of freedom (129). The values ranging from 0-25% were considered as a low heterogeneity, from 26-50% as a moderate, and above 50% as a substantial heterogeneity between the studies (129).

The difference in meta-estimates between study designs and between subgroups were tested by fitting meta-regression models (method of moments) and by conducting Wald's tests.

The risk of publication bias was tested by visual inspection of funnel plots presenting log-transformed effect estimates and its standard errors, and with Egger's, and Begg's tests at 10% significance level (130).

4 Results

4.1 Paper 1

During an average of 13.1 years of follow-up of 91 767 women, 9675 cases of cancer were diagnosed: 3277 (33.9%) breast cancers, 1266 (13.1%) colorectal cancers, 446 (4.6%) ovarian cancers, and 819 (8.5%) lung cancers.

Compared to light coffee consumers ($\leq$1 cups/day), women who drank more than 3 and up to 7 cups/day had a 17% reduced risk of colorectal cancer (95% CI 0.70-0.98, $p_{\text{trend across categories}}$=0.10) and a 9% reduced risk of cancer at any site (95% CI 0.86-0.97, $p_{\text{trend across categories}}$=0.03). A significantly increased risk of lung cancer was observed in women who were heavy coffee consumers (>7 cups/day) compared to light coffee consumers (HR=2.01, 95% CI 1.47-2.75, $p_{\text{trend across categories}}$<0.001). However, no statistically significant association was observed in never smokers (>5 cups/day vs. $\leq$1 cups/day HR=1.42, 95% CI 0.44-4.57, $p_{\text{trend across categories}}$=0.30). No significant association was found between coffee consumption and the risk of breast or ovarian cancer.

The results from the complete-case analyses were similar to those from the analyses of multiple imputed datasets. We did not find evidence of violation of proportional hazards assumption. None of the interactions tested reached statistical significance. After we excluded breast cancer cases diagnosed during the first two years of follow-up, we found significantly decreased risk of breast cancer for low and high moderate coffee consumers compared to light consumers (HR=0.90, 95% CI 0.81-0.99; HR=0.86, 95% CI 0.78-0.96, $p_{\text{trend across categories}}$=0.01).

4.2 Paper 2

The average follow-up of 145 247 women and 48 192 men was 13.6 years of follow-up. During more than 2.6 million person-years, a total of 19 733 cancer cases were identified, out of which 479 (2.4%) were bladder cancers, 97 (0.5%) esophageal cancers, 475 (2.5%) kidney cancers, 491 (2.5%) pancreatic cancers, and 281 (1.4%) stomach cancers.

Compared to light filtered coffee consumers ($\leq$1 cup/day), heavy filtered coffee consumers ($\geq$4 cups/day) had 26% reduced risk of being diagnosed with pancreatic cancer (95% CI 5%-43%, $p_{\text{trend across categories}}$=0.01). We did not observe significant associations between total or boiled coffee consumption and any of the investigated cancer sites, neither in the entire study sample nor in analyses stratified by sex. The reduced risk of pancreatic cancer was confined to never smokers (moderate vs. light filtered coffee consumers HR=0.60, 95% CI 0.41-0.87; heavy vs. light filtered coffee consumers HR=0.60, 95% CI 0.35-1.01; $p_{\text{trend across categories}}$=0.01).

27

Women who drank more than 1 and up to 4 cups of boiled coffee per day had a HR of 1.58 (95% CI 1.03-2.05) compared to light boiled coffee consumers. However, no association was found for women who drank more than 4 cups of boiled coffee, nor we found a statistically significant dose-response relationship. We found an increased risk of bladder cancer among never smokers who were heavy filtered coffee (HR=1.87, 95% CI 1.01-3.45, $p_{\text{trend across categories}}$=0.03) or heavy total coffee consumers (HR=1.86, 95% CI 1.12-3.10, $p_{\text{trend across categories}}$=0.08), and an increased risk of stomach cancer in never smokers who were heavy boiled coffee consumers (HR=2.14, 95% CI 1.10-4.16, $p_{\text{trend across categories}}$=0.04).

No significant departure from linearity between filtered, boiled, and total intake and the study outcomes was found. The test of Schoenfeld residuals did not indicate a violation of the proportional hazards assumption. We found no evidence of effect modification between coffee consumption and BMI for any of the outcomes. The estimates for stomach cancer became stronger in the analyses performed after we excluded cases diagnosed during the first year of follow-up.

4.3 Paper 3

Twelve cohort (131-142) and eight case-control (143-150) studies were eligible for inclusion, contributing with 11 663 and 2 746 endometrial cancer cases, respectively. The summary RR for highest compared with lowest coffee intake category was 0.73 (95% CI: 0.67–0.80; $p_{\text{heterogeneity}} = 0.051$, $I^2 = 36.7\%$) after combining results from the cohort and case control studies. The corresponding summary RR among cohort studies was 0.76 (95% CI: 0.69–0.83; $p_{\text{heterogeneity}} = 0.06$, $I^2 = 40.5\%$) and 0.63 (95% CI: 0.53–0.76; $p_{\text{heterogeneity}} = 0.57$, $I^2 = 0\%$) for case-control studies. One-cup increment per day was associated with 3% risk reduction (95% CI: 2% -4%) in cohort studies and 12% (95% CI: 5% -18%) in case-control studies. We did not observe a statistically significant difference between the estimate from cohort and case-control studies (p=0.1), after applying a meta-regression model. We found evidence of an under-representation of smaller studies after a visual inspection of a funnel plot.

After pooling the results from five cohort studies, the association remained significant only in women with body mass index over 30 (RR=0.71, 95% CI: 0.61-0.81). The summary RR for high vs low coffee consumption categories in postmenopausal women was 0.71 (95% CI: 0.62-0.81, $p_{\text{heterogeneity}} = 0.394$, $I^2 = 4.2\%$). In cohort studies, a significant protective RR was observed for ever smokers (RR = 0.67, 95% CI: 0.49-0.92; $p_{\text{heterogeneity}} = 0.005$, $I^2 = 73.5\%$), never smokers (RR = 0.78, 95% CI: 0.67-0.92; $p_{\text{heterogeneity}} = 0.302$, $I^2 = 17.2\%$) and former smokers (RR = 0.80, 95% CI: 0.66-0.97; $p_{\text{heterogeneity}} = 0.332$, $I^2 = 0\%$).

Inverse associations to risk of endometrial cancer were observed in sub-analyses of cohort studies for caffeinated (RR= 0.64, 95% CI: 0.49-0.83; $p_{\text{heterogeneity}} = 0.088$, $I^2 = 50.8\%$), decaffeinated coffee (RR= 0.73, 95% CI: 0.59-0.90; $p_{\text{heterogeneity}} = 0.732$, $I^2 = 0\%$), and in never users of postmenopausal hormone

therapy (RR=0.59, 95% CI: 0.49-0.73; $p_{heterogeneity} = 0.579$, $I^2 = 0\%$). A negative association between high coffee intake and endometrial cancer risk was further observed across different geographical regions (Europe, Asia, North America). The association between coffee consumption and EC risk was attenuated when we conducted meta-analyses using the alternative approach in which we compared moderate/heavy vs never/low coffee consumers.

5 Discussion

5.1 Summary of the results

In paper 1, a decreased risk of cancer at any site was associated with high moderate coffee consumption. We found a statistically significant association between high coffee consumption (>7 cups/day) and increased risk of lung cancer. However, residual confounding due to smoking may have contributed to the association between high coffee consumption and the risk of lung cancer.

The data from the joint NOWAC and NSHDS cohort suggest that high filtered coffee consumption might reduce the risk of pancreatic cancer. No evidence of an association was found between coffee consumption and the risk of esophageal or kidney cancer. The positive association between bladder cancer risk and boiled coffee consumption in women who were moderate boiled coffee consumers was not supported by the findings from the dose-response analysis. Further, the increased risk of bladder and stomach cancer was found in never smokers.

The results from the meta-analysis strengthen the evidence of a protective effect of coffee consumption on the risk of endometrial cancer and suggest that the effect of coffee intake is particularly beneficial for women with obesity.

5.2 Discussion of methodology

5.2.1 Methodological considerations in prospective cohort design

5.2.1.1 Selection bias

Selection bias occurs when a sample of study participants is not representative of the source population from which the sample was derived from, i.e. if there are systematic differences between those that participate in a study and those who do not (151). Several concerns can be raised in case of high percentage of non-responders. For example, if there are differences between responders compared to non-responders when it comes to demographics, life-style, health or diet.

The response rate of 52.7% in the NOWAC cohort and the participation rate of 48-79% in the sub-cohorts of the NSHDS study are similar to those in other population-based cohorts (152). The higher response in the NOWAC cohort was observed in the age-groups 30–34 years till 55–59 years (60%), while 44.7% responded among those aged 65–70 years (115, 152). The authors of a validation study of the cohort found no differences in oral contraceptive use, parity, and the level of education between the responders and the non-responders. Moreover, the study participants did not differ from the source population except for somewhat higher educational level (152).

Similarly, in the VIP cohort, only limited evidence of selection bias related to income, age, and unemployment was found. In both genders, the youngest group was less represented among participants. Participation was also lower in those that were unemployed compared to the employed, and in individuals that were in the lowest income level (153).

The quality assessment of the MONICA project revealed that compared to participants, non-participants were more often regular cigarette smokers, had somewhat lower BMI, and that a smaller proportion were married or cohabitant. No substantial differences were found in level of education (154, 155). Overall, the authors of the quality assessment conclude that the data from the MONICA cohort is of good quality (154, 156).

Somewhat higher level of education observed in the NOWAC cohort, and the lower participation rates of those with a low income in the VIP cohort might have resulted in the measure of association between coffee intake and the risk of cancer that is, to an unknown degree, different from the source population due to a underrepresentation of heavy coffee consumers. Highly educated women in the NOWAC are less likely to be heavy smokers compared to lower educated women. As there is an observed positive correlation between smoking exposure and coffee intake, i.e. heavy smokers are more likely to be a heavy coffee consumers, this indicates that highly educated women drink less coffee compared to women with fewer attained years of education. Similar conclusion might be drawn in regards to the VIP cohort, as smoking and other forms of tobacco use are much higher among those with lower income, the group that was less likely to participate in the survey (157). Finally, as the non-participants in the MONICA cohort were more likely to be active smokers, it might be speculated that heavy coffee consumers are slightly underrepresented in the NOWAC and the NSHDS cohorts.

5.2.1.2 Information bias

Information bias arises in an epidemiological study when systematic errors in measurements of exposure and/or outcome have occurred (158). Measurement errors of exposure can result in misclassification which can be divided in two groups. A non-differential misclassification is the result of measurement error of an exposure that occurred among participants independently of the study outcome. Contrary, a differential misclassification occurs when the extent of measurement error is different for those study participants with a disease and those without (151).

As the data on coffee consumption and other covariates were collected from self-administered food-frequency questionnaires (FFQ), a misclassification of a certain degree is possible. However, the FFQs used in the NOWAC cohort were validated by 24-hours dietary recalls study. The results from the validation study showed a high validity of information on coffee consumption (Spearman's correlation coefficient r=0.82) (159). Moreover, a physical activity scale used to measure physical activity in NOWAC women, self-reported history of diabetes mellitus, as well as anthropometric measures, all

31

were shown to be reliable based on the results from the validation studies (160-162). Validation of food-frequency questionnaire measurements in the Northern Sweden Health and Disease cohort has shown that consumption frequencies of coffee were similarly measured by FFQ and 24-hours dietary recall regardless of preparation method (Pearson's product moment correlations ranging between 0.72 and 0.84) (163).

In paper 1, we decided to use follow-up information on coffee consumption and on smoking exposure as the main confounder in order to take into account any intrapersonal variations that might have occurred during a follow-up of twenty years and thus reduce the risk of misclassification bias.

In both NOWAC and NSHDS cohorts, we lacked information on certain types of coffee drinks such as espresso, cappuccino, café latte, macchiato, or decaffeinated coffee as these brewing methods were not asked about in the questionnaires. Even though a consumption of these coffee types was uncommon in Norway and Sweden at the time of data collection, it is still possible that total coffee consumption was underestimated for some of the participants, thus resulting in misclassification that is most likely to be non-differential. We also did not have information on instant coffee consumption from the NSHDS cohort. As instant coffee is prepared by freeze-drying filtered coffee, from a chemical point of view, this distinction is of less importance from a misclassification of brewing technique perspective. However, due to a lack of information on instant coffee intake, the total coffee consumption in Swedish cohort was somewhat underestimated.

When self-reported, smoking exposure measures such as smoking status, number of cigarettes smoked per day, or duration of active smoking are particularly prone to measurement errors as smoking prevalence is often underestimated (164). Indeed, in the sample from paper 1, we observed 1 722 women that reported being ever smokers at baseline and never smokers at follow-up, and the misclassification of this sort is unlikely to have occurred only in follow-up data. The observed risk estimates might have been stronger for the outcomes that were inversely associated with coffee consumption if the true distribution of smoking status was available from our data, whereas in case lung cancer risk, the observed positive association would have been weaker. We did not update information on other covariates other than coffee consumption and smoking exposure variables in paper 1. As the number of missing data in all covariates on follow-up was around 30%, we lacked computational power to perform multiple imputation on all the variables at both baseline and the follow-up. However, we conducted a complete-case analyses for all of the outcomes in which we had updated information on all of the covariates included in the analyses. The estimates from these analyses did not differ from the main results. For similar reasons, we could not use the repeated information from the third round of questionnaires in the NOWAC study in paper 1, nor have we updated information on the main exposure or covariates in paper 2. Due to proportion of missing in the NOWAC cohort for almost all of the covariates in the third measurement exceeding 50%, and the

analytical sample size in the paper 2 was close to 200 000 participants, we estimated that the multiple imputation for a single outcome would exceed 300 CPU (central processing unit) hours, and that the memory requirements would greatly exceed the capacities of a standard desktop computer. Therefore, due to a lack or incomplete update of the variables, some misclassification in papers 1 and 2 is probable, as it is unlikely that the study participants were drinking the same amount of coffee throughout the study period of 20 years. Moreover, the time-varying effect of covariates should be taken into account in an analysis, and the lack of proper adjustment in this regard could have led to biased estimates (165). Finally, further misclassification might have been introduced due to the different units of measurement of coffee consumption between the Norwegian and Swedish (occasions/day vs. cups/day), and due to individual variation in cup size.

A misclassification in our studies, as in other cohorts, is more likely to be non-differential, as the data were collected before the outcome of interest has occurred. As a result, the observed effect estimates of an association between coffee consumption and the risk of studied outcomes might have been underestimated.

A misclassification of outcome in the NOWAC cohort is less likely to have occurred and would have a small impact on the estimates, as the Cancer Registry of Norway is considered to be reasonably accurate and close-to-complete (98.8%) (166). Furthermore, the observed incidence rates for cancer sites in the NOWAC study were comparable to national figures (115, 152). At the same time, it is estimated that 99% of the cancer cases in the Swedish Cancer registries are morphologically verified and that the registry is generally considered to be of good quality (167). Further, cancer incidence rates in the VIP cohort do not differ from the figures in the population of Västerbotten at large (168). Therefore, the chance of misclassification of outcomes in papers 1 and 2 was minimal.

5.2.1.3 Confounding

A confounder is a factor that is associated with both study outcome and exposure of interest, and does not stand in the intermediate pathway of causation between the exposure and the outcome. Failing to adjust for a confounding effect in analyses can result in biased estimates in both directions and consequently erroneous conclusions (151). This might occur due to measurement error of a confounder, presence of undetected confounder, or suboptimal building of a regression model (169). Residual confounding occurs when the distortion of an estimate remains even after controlling for confounding by a measure of the confounding factor in the analysis.

In all of our analyses, we *a priori* chose a set of potential confounders from the available literature. A potential confounder was included in the final model if its removal led to a change in the regression coefficients of at least 10% in any of the coffee consumption groups. This approach, however, can fail to identify a variable as a confounder if a measurement error of said variable has occurred (170).

Moreover, from a simulation study by Lee, cutoff points for the change-in-estimate criterion vary according to the effect size of the association between exposure and outcome, sample size, standard deviation of the regression error, and exposure–confounder correlation (171). Consequently, a possibility of residual confounding in paper 1 cannot be excluded.

We lacked information on tea consumption in the NOWAC cohort since this information was not available from the questionnaires. As tea and coffee share many bioactive components, a confounding effect of tea consumption might be present which therefore might have confounded a true association between coffee consumption and the risk of cancer. Furthermore, in the NOWAC cohort, we did not have information on family history of cancer other than a breast cancer. If the family history of studied cancer outcomes was indeed related to coffee consumption, this could have introduced residual confounding in both paper 1 and 2.

In paper 2, we lacked additional information on smoking exposure such as number of cigarettes smoked per day, number of pack-years, and/or duration of smoking in years in the Swedish cohort and information on family history of cancer was not available in neither of the two cohorts. However, as we did not observe any significant positive association between coffee consumption and the risk of five cancer sites, we believe that additional adjustment for aforementioned factors would not change our conclusions.

The residual confounding by smoking might have particularly biased the estimates for the observed positive association between heavy coffee consumption and the risk of lung cancer. It is now well established that caffeine metabolism is accelerated in cigarette smokers and that the caffeine clearance is shorter among those who smoke (172-174). This implies that smokers need to consume more coffee in order to experience the same effect of caffeine as those who do not smoke. Indeed, we observed significant differences in coffee consumption between never, former, and current smokers in the cohort, with 68.5% of heavy coffee consumers being current smokers. We decided to use repeated measurements on smoking variables in order to adjust optimally for smoking exposure. However, we did not have information about such markers of smoking exposure as if a person inhales smoke from a cigarette, or lifetime exposure to secondhand smoke and other pollutants that would allow proper adjustment. In order to check if the positive association between heavy coffee consumption and the risk of lung cancer was indeed true, we performed a subgroup analysis on never smokers. Only after observing a non-significant association in this subgroup, we could suspect that residual confounding due to smoking may have contributed to the positive association in the analysis of the entire cohort.

Additional residual confounding might be due to misclassification of the adjustment variables above discussed. If, for example, current smokers were classified as former smokers in the lung cancer analysis, this misclassification would strengthen the positive association between coffee consumption

and the lung cancer risk. Finally, modelling of continuous variables could have been a source of residual confounding in our analyses. If the association between a confounder and the outcome is not linear, the assumption of a linear relationship between the confounder and outcome specified in a model can result in inadequate control for confounding (175).

5.2.1.4 Effect modification and reverse causality

Effect modification occurs when two factors interact to change the risk of an outcome (151). For example, if smoking status modifies the effect of coffee intake on risk of lung cancer this would indicate that the association between coffee and lung cancer risk is different in never and ever smokers. Usually, in statistical analysis, effect modification is assessed by including a product of two variables (interaction term) that might interact in a regression model.

We checked for possible interactions between coffee consumption and smoking status, BMI, and physical activity level in paper 1, and between coffee consumption and BMI in paper 2. The choice of these variables was based on their potential to either interact with the antioxidant effects of coffee, or affect the metabolism of coffee ingredients (176-178). Even though we did not observe any statistically significant effect modification, it should be noted that the interaction analysis are often underpowered as the number of cases within some of the subgroups could be insufficient in order to detect significant risk differences.

Reverse causality is a phenomenon in which rather than an exposure influencing an outcome it is that the outcome is influencing the exposure or changes in the exposure. To illustrate, symptom of undiagnosed stomach cancer or precancerous lesions such as nausea, gastric reflux, vomiting can make a study participant change their hot beverage intake several years before the disease is actually diagnosed. Thus, the reported coffee consumption couple of years prior to diagnosis would not reflect a true long-term consumption. To take into account possible reverse causality, a usual approach is to conduct a sensitivity analysis in which cancer cases diagnosed during the first one or two years of follow-up are excluded. The estimates from this analysis are than compared to the estimates from the entire sample.

In paper 1, the use of the updated information on coffee consumption made it possible to conduct extensive analyses in order to check for possible reverse causality. First, we performed sensitivity analyses after excluding cancer cases at the corresponding sites that were diagnosed during the first two year of follow-up. We then repeated the analyses after we had excluded cancer cases that occurred during the first year of follow-up, and at the same time censoring at the time of answering the second questionnaire those cancer cases diagnosed during the first year after they received the second questionnaire. No significant departures between the estimates from the reduced and complete samples were detected. In paper 2, we repeated the analyses after we excluded cancer cases of interest

diagnosed during the first year of follow-up. The exclusion of cases resulted in somewhat stronger association only between coffee consumption and stomach cancer risk, indicating that coffee habits have changed with the onset of the stomach cancer symptoms in at least some of the participants that were diagnosed with the disease.

5.2.1.5 Multiple imputation

Researchers usually address missing data by including in the analysis only complete cases —those individuals who have no missing data in any of the variables required for that analysis. However, results of such analyses can be biased. Furthermore, if the data are missing in several variables, the cumulative effect of missing data can lead to considerable reduction of the original sample, which in turn causes a substantial loss of precision and power (119). Conversely, single imputation methods, such as imputations with mean, median, or mode, although usually easy to perform, often lead to biased effect estimates and underestimation of standard errors, as these methods does not take into account uncertainty for the missing values (119, 179).

There are three major types of missing: missing completely at random (MCAR), missing at random (MAR), and missing not at random (MNAR). Under the MCAR mechanism, there are no systematic differences between the missing values and the observed values i.e. the probability/reason of an observation being missing is independent of observed and unobserved infomation. Missing at random mechanism implies that systematic difference between the missing and the observed values can be explained by differences in observed data. Finally, if a missingness mechanism is missing not at random, then systematic differences remain between the missing values and the observed values, even after the observed data are taken into account (119). Unfortunately, it is not possible to distinguish between different missingness mechanisms without additional untestable assumptions (180).

A complete-case analysis is valid if the missingness mechanism is MCAR, and can also be valid in certain situations under non-MCAR mechanisms. Specifically, if the reasons for the missing data in predictor variables are unrelated to the studied outcome, then analyses of complete cases will give unbiased results (119, 181). Multiple imputation will yield an unbiased estimates if the missingness mechanism is either MCAR or MAR, although there have been proposed methods for multiple imputation of MNAR data that would produce valid estimates and its standard errors (119, 182).

Multiple imputation by chained equations (MICE) is a flexible and practical approach to generate imputations based on imputation models (183, 184). The MICE involves series of regression models from which missing data in a variable are replaced by simulated draws from the corresponding posterior predictive distribution of said variable. This means that each variable is modeled according to its distribution - binary variables modeled using logistic regression, ordinal variables modeled using ordinal logistic regression, and continuous variables modeled using linear regression or predictive

mean matching (183, 184). In other words, if we denote variable with missing value as x_1, then the observed values on x_1 are regressed (based on their posterior distribution) on the other variables specified in the imputation model, restricted to individuals with the observed x_1. The missing values on x_1 are then replaced by simulated draw from the posterior predictive distribution of x_1, i.e. with the prediction from the regression model (183, 184). The subsequent step involves regressing the second variable with missing values, x_2 on all other variables specified in the imputation model, using previously imputed values of x_1, and restricted to individuals with the observed x_2, and then replacing missing values from the posterior predictive distribution of x_2. After these steps are repeated for all other variables with missing data, one cycle or iteration has been completed (184). To create one imputed dataset, 10 iterations are usually performed in order to stabilize the results (default in STATA) (184). It is usually recommended that no less than twenty datasets be imputed in order to reduce sampling variability from the imputation simulation (119). The estimates from the imputed datasets are then combined using Rubin's rules to obtain point estimates and their standard errors as described in 3.1.7.

As the proportion of missing data at follow-up was high (e.g. number of pack-years 42.8%), we performed MICE in order to deal with the missing data. We imputed missing information at baseline and follow-up under the assumption that data was missing at random, i.e. the probability/reason of an observation being missing is independent of unobserved infomation. We created twenty duplicate datasets for each outcome, with ten iterations per dataset for the burn-in period. Further, for each of the cancer outcome, we created separate imputation models that consisted of broad specter of variables, outcome indicator, interaction terms, and Nelson-Aalen cumulative hazard estimator in order to increase the predictive power of the imputation procedure (185). The possibility remains that at least some of the data was missing not at random, i.e. that their probability of being missing is dependent on unobserved information, which would make estimates calculated from the imputed datasets not free of bias. Furthermore, we did not have enough CPU power to impute more than twenty datasets for each of the outcomes, which would further reduce sampling variability and provide more stable estimates.

As the estimates from the complete case analyses and the analyses from multiple imputed datasets were similar, it might be speculated that missingness mechanism was a case of missing at random in which missingness was driven by the explanatory variables, and given these, not the outcome (119) However, even if a missingness mechanism is assumed to be the special case of missing at random, a multiple imputation should be performed as a sensitivity analysis in order to check if the estimates between complete case analysis and the analysis of multiple imputed datasets are similar.

5.2.1.6 Non-linearity and restricted cubic splines

A continuous variable as a predictor in a regression model assumes that there is a linear relationship between the predictor and an outcome. If this assumption is not true, then the regression model will be misspecified, i.e. the model will fail to show a true relationship between the predictor and the outcome (186). Categorizing a continuous variable is the most simple and frequently used method to investigate non-linearity. However, in this approach the effect of the predictor on the outcome is constant within each strata of categorized predictor. More so, by using cut-off points, it is not possible to estimate a smooth function between the predictor and the outcome from the model (186).

Two flexible ways of addressing possible non-linear relationships are by applying restricted cubic splines or fractional polynomials models that allow flexible parametrization of a continuous variable (187). With restricted cubic splines, a continuous variable is still used in a model, but it is transformed in a way that produces linear relationship (186). The continuous predictor is divided into set of intervals, with the boundaries of the intervals being defined by the *knots*. Within each interval a cubic polynomial (polynomial of degree 3) function is fit. There are three continuity restrictions that are applied (187). First, if the assumption is that the function changes smoothly over time, then the estimated functions are forced to join at the knot locations. Second, the first derivate of the spline function, i.e. the gradient of the function, is also forced to agree at the knots. Final restriction is to force the second derivate, i.e. the rate of change in the gradient, to agree at the knots locations as well (187). Finally, the splines are restricted to be linear in the two tails, i.e. the function is forced to be linear before the first knot, and after the last knot locations (186). Cubic splines require k + 3 (where k is the number of knots) coefficients to be calculated in addition to the intercept, compared to 1 coefficient in a linear model (186).

The recommended number of knots is usually four to five (118, 188). Harrell suggests that three knots should be used if the sample size is small, three knots should be used so that enough observations between the knots are available to fit a polynomial function. If the sample size allows and if the relationship between a predictor and an outcome changes quickly, more than five knots can be used (118, 186). The location of the knots should ensure that there are sufficient number of observations between the knots to estimate the cubic polynomial (186).

In papers 2 and 3, we modelled restricted cubic splines in order to assess a possible non-linear relationship between coffee consumption and the study outcomes. In paper 2, we modeled restricted cubic splines with four knots, with their locations based on Harrell's recommended percentiles of the total and filtered coffee consumption. Harrell's recommendation suggests placing knots at equally spaced percentiles of the original variable's marginal distribution, and involves an additional restriction that the smallest knot may not be less than the fifth-smallest value of a predictor and the

largest knot may not be greater than the fifth-largest value of a predictor (118). The restricted cubic splines for boiled coffee were modeled with three knots, positioned at the 25th, 60th, and 95th percentiles of the coffee distribution. In paper 3, we modeled restricted cubic splines with three knots for both cohort and case-control studies, and the location of the knots was based on Harrell's recommendations. In both papers, we used values of Akaike information criterion to ensure that the number and the location of the knots indeed best fit the data (189). In general, increasing number of knots from four to five in paper 2, and from three to four in paper 3, led to overfitting the data, whereas the changes of the knots' location had less impact on the shape of the estimated function and the parameter estimates.

5.2.1.7 External validity

External validity is defined as "the degree to which results of a study may apply, be generalized, or be transported to populations or groups that did not participate in the study" (190). As discussed in 3.1.1, Norwegian women in the NOWAC cohort were randomly drawn from the population registry. Lund et al. concluded that the NOWAC cohort is externally valid as only negligible differences were found in level of education between study participants and the source population (115, 152, 191). Further, as mentioned previously, the incidence rates for all cancer sites in the NOWAC were almost identical to the figures from the Norwegian Cancer Registry (115, 152).

The participants in the MONICA cohort were also randomly selected from the population registries. The participation rate of 60% in the VIP cohort and over 60% in the MONICA cohort along with no substantial differences in cancer incidence rates between the VIP and the figures in the population of Västerbotten (168) indicate that the external validity of NSHDS cohort is satisfactory.

5.2.1.8 Other considerations

In both papers 1 and 2 we used participants age as the underlying timescale. Some studies have shown that this approach is more appropriate for survival analysis compared to using time-on-study as time scale and then adjusting for participants' age in a Cox model (192, 193).

The proportional hazards (PH) assumption assumes that survival curves for different strata have hazard functions that are proportional over time. To our knowledge, in STATA before version 14, it was not possible to conduct the test of Schoenfeld's residuals on m imputed datasets together, but rather on individual imputed datasets. Therefore, in paper 1, we checked the assumption by testing an interaction between coffee consumption and the logarithmic transformation of participants' age. In paper 2, the PH assumption was checked by testing Schoenfeld's residuals. In both papers, the assumption seemed not to be violated. However, statistical power to detect a violation of the PH assumption can be low to moderate even when the observed number of failures is high (194).

Finally, some of the analyses performed for certain outcomes performed were statistically underpowered which consequently could have led to failure to detect the effect of coffee consumption on the risk of some cancer sites when the effect was actually present. Specifically, in paper 1 the number of cases of lung cancer in the subgroup analysis according to smoking status was very low in never smokers. Similarly, in paper 2, the small number of cases hampered the analyses of esophageal cancer. Further, subgroup analyses by smoking status were underpowered in the analyses of bladder, esophageal and stomach cancer sites, an issue that was, again, more pronounced in never smokers.

5.2.2 Methodological considerations in meta-analyses

5.2.2.1 General considerations

The limitations in the review are mainly related to the limitations of the individual studies included in the meta-analysis. In all of the studies, coffee consumption was self-reported through food-frequency questionnaires, with six studies overall not reported using validated FFQs. Therefore, the possibility of misclassification cannot be disregarded. Even though we restricted our meta-analysis to include only studies that adjusted for BMI and smoking status, and all but three cohort and one case-control study adjusted for some of the reproductive/menstrual factors, the presence of unknown confounders could have influenced the estimates.

Additionally, some of the limitations were specific for case-control studies. Selection bias should be considered in interpreting the results from these studies. In order to minimize bias, controls from case-control studies should be representative of the population from which the cases were derived (151). As three of the included case-control studies included hospital-based controls, which might not be representative of the underlying source population, selection bias cannot be excluded. In order to check if the pooled estimates were different between hospital-based and population-based case-control studies, we conducted subgroup analyses based on a selection of controls. We did not find a difference in the pooled estimates between population based and hospital based studies.

Case-control-studies suffer to a different extent from recall bias. Recall bias arises "when participants in a study are systematically more or less likely to recall and relate information on exposure depending on their outcome status, or to recall information regarding their outcome dependent on their exposure" (195). As a consequence, misclassification of coffee consumption could have occurred in the reviewed case-control studies. This would further warrant caution when communicating the results pooled from the studies with this design. However, even though the possibility of recall bias in case-control studies cannot be excluded, it can be argued that the participants in these studies would not assume that coffee drinking might influence the risk of endometrial cancer, and therefore would be less likely to either underreport or over report their coffee drinking habits.

We decided to pool the results from both cohort and case control studies for several reasons. As endometrial cancer is a rare outcome, odds ratios from case-control studies will resemble risk ratios from cohort studies. Further, studies with a different design might be attempted when studies are addressing a common question (196). Nevertheless, we did provide separate results for the case-control and cohort studies as well as pooled results, and a meta-regression model did not reveal significant differences between the estimates from cohort and case-control studies.

5.2.2.2 Statistical heterogeneity

Heterogeneity is defined as any kind of variability between the studies that are included in a meta-analysis. The sources of variability might be due to a diversity of study participants or methodological diversity between the studies, such as different study designs, use of repeated measurements, difference in regression models, or use of different cut-off points when defining categories of a main exposure (197).

We assessed the heterogeneity between included studies by calculating I^2 statistics. The value of I^2 represents the percentage of variability in meta-effect estimates that is actually due to heterogeneity between studies and not sampling error. Interpretation of the I^2 statistics should also take into account magnitude and direction of effect of studies, and strength of evidence for heterogeneity, i.e. p value from the chi-square test (129). There are several strategies to address heterogeneity when present. One of them is to perform a random effect meta-analysis. This type of analysis, unlike fixed-effect meta-analysis, incorporates the assumption that the effects from the different studies are not identical but follow some distribution. As random effect model acknowledges the uncertainty on that the effect estimates between the studies are different (by treating the differences as random), the confidence interval around meta-effect estimates will be wider compared to a fixed-effect method, but only in the presence of heterogeneity (197). The other methods to tackle heterogeneity include exploring the heterogeneity by conducting sub-group analyses, changing the effect measure, excluding studies, or finally, not performing a meta-analysis altogether (197).

To assess the level of heterogeneity based on the I^2 statistics, we used cut-off points described in 3.2.2. All the meta-analyses were performed by the random effect method, and we conducted numerous subgroup analyses, to both further explore the effect of coffee consumption and the risk of endometrial cancer, and to investigate the observed moderate heterogeneity in the main meta-analysis. Even though the results from Paper 3 consistently indicate a protective effect of coffee intake on the risk of endometrial cancer, some caution should be exercised when interpreting the magnitude of this effect due to a moderate level of heterogeneity between the studies. Moreover, even though the I^2 statistics is generally considered independent of the number of studies included in analysis, a recent study has

shown that the values of I^2 statistics should be interpreted cautiously if a meta-analysis includes few studies, as the confidence interval around these values are often very wide (197, 198).

In paper 3, we observed substantial heterogeneity ($I^2 > 50$) in seven of the pooled analyses, in addition to six more analyses in which heterogeneity between the studies was moderate (I^2 between 26 and 50). Interestingly, the meta-analyses that included both study designs had level of heterogeneity that was almost identical to the meta-analyses which included only cohort studies (32.0% vs 31.9%), contrary to the meta-analyses of case-control studies in which no heterogeneity between the studies was observed. However, the heterogeneity in subgroup analyses that involved both study designs was at least moderate in all but three analyses. In general, heterogeneity between case-control studies seemed lower than between studies with prospective cohort design. Heterogeneity was low in the analyses of studies from the same geographical region (United States, Europe, Asia) and was distinctively high in the subgroup analyses of current smokers, those with BMI over 25, as well as in the analyses of caffeinated coffee. As already suggested, differences in methodological choices that were made by the study authors, such as cut-off points that defined coffee-consumption categories, or adjustment factors that were included in analyses might have been the underlying reason for the observed levels of heterogeneity in our meta-analyses. Substantial heterogeneity that accompanied the analyses of overweight/obese women might be explained by the methodological approach that we used to combine the results. As described in 3.2.2, we combined category specific estimates among coffee drinkers within each study into a single estimate for moderate to heavy coffee drinkers' using a fixed effect model, after which we pooled single estimates using a random-effects model. As some studies have reported coffee estimates for BMI categories 25-30 and above 30 separately, while other studies only reported the estimates for those with BMI above 25, this discrepancy could have been the reason of substantial heterogeneity between the studies, which was also found in the study by Lafranconi et al. (93).

5.2.2.3 Publication bias

Publication bias is a subtype of reporting bias which occurs when the dissemination of findings, mainly through publications, is influenced by the nature and direction of results (199). In their methodological review, Hopewell et al. found that randomized controlled trials with positive results had almost four times higher odds of being published compared to results that were not statistically significant (200). We performed a thorough search of the MEDLINE and EMBASE databases for relevant publications, and also checked references of previously published similar meta-analysis. A visual inspection of funnel plots, Egger's, and Begg's tests were used to assess the risk of publication bias. A funnel plot represents a scatter plot between log-transformed effect estimates (usually x axis) and standard errors of the estimates from the included studies (y axis). Any kind of asymmetry of a funnel plot could indicate a publication bias. Other than by visual inspection, asymmetry of a funnel

plot can be tested with Egger's and Begg's tests, which if significant at recommended 10% level could also raise an alarm regarding publication bias (199).

If observed, however, asymmetry of a funnel plot does not necessarily need to be due to publication bias. Some reasons include poor methodological quality of smaller studies, a heterogeneity between studies, artefact, or chance alone. Statistical tests for checking a funnel plot asymmetry could also be misleading. The Egger's test is usually not recommended for testing funnel plot asymmetry if the number of the included study is fewer than 10 or in the presence of a significant heterogeneity between the studies (199).

Even though we did observe a substantial asymmetry of the funnel plot, indicating an under-representation of smaller studies reporting positive associations between coffee consumption and the risk of endometrial cancer, it is likely that the asymmetry accurately reflects a lack of positive association, further suggesting lack of carcinogenicity for the association between coffee drinking and endometrial cancer (83).

5.3 Discussion of the main results

5.3.1 Paper 1

5.3.1.1 Cancer at any site

The results from paper 1 regarding the association between coffee consumption and the risk of cancer overall are in agreement with the results from the meta-analysis by Yu et al. (201). The authors found that women in the highest coffee consumption category had 13% lower risk of being diagnosed with any type of cancer compared to women in the lowest consumption category. In a prospective study from Norway, Stensvold and Jacobsen reported a statistically non-significant inverse association with cancer risk in women who consumed at least 7 cups/day, compared to women whose intake was no more than 2 cups/day (85).

Although we did not observe statistically significant associations in all of the coffee consumption categories, indication of dose-response was observed based on a trend test suggesting that coffee consumption might reduce the risk of cancer overall. Even though the main analysis was adjusted for smoking status, number of pack-years and the age of smoking initiation, residual confounding could be the reason behind the lack of association in the highest coffee consumption category.

As discussed in 1.1.2, a variety of biologically active substances contained in roasted coffee have the potential to either suppress or induce carcinogenesis. Chlorogenic acid is one of the ingredients that contributes significantly to the antioxidant effect of coffee. It has been hypothesized that chlorogenic

acid could alter the risk of some cancers by reducing glucose levels in the blood and increasing insulin sensitivity (62, 64). Polyphenolics from sweet potatoes, that consist of caffeic acid, chlorogenic acid, 3,4-di-O-caffeoylquinic acid, 3,5-di-O-caffeoylquinic acid, 4,5-di-O-caffeoylquinic acid, and 3,4,5-tri-O-caffeoylquinic acid, were found to suppress growth of human cancer cells (202). Chlorogenic acid was further found to have inhibitory effect on colon carcinogenesis in male rats (203). One of the proposed molecular mechanisms of antitumor effect of chlorogenic acid is that this coffee compound is inducting genes GSK-3β, APC, and inhibits gene β-catenin which promote tumor cell apoptosis in the Wnt pathway (204).

Some of proposed anticarcinogenic mechanisms of kahweol include inducing apoptosis in human leukemia cells and synthesis of endogenous antioxidants (41, 43), and reducing genotoxicity in hepatoma cells (42). Further, kahweol was found to induce apoptosis of colorectal cancer cells in human by upregulating activating transcription factor 3 (205). Cafestol and kahweol were also reported to prevent genotoxic effect of N-nitrosodimethylamine and 2-amino-1-methyl-6-phenylimidazol, carcinogens found in human diet, and to have protective effect against aflatoxin B1-induced genotoxicity (42, 206). Finally, coffee diterpenes modify the effect of hepatic *N*-acetyltransferase and glutathione *S*-transferase activity, which further contributes to chemoprevention against cancer (207).

Caffeine could affect the risk of malignancies in pre- and postmenopausal women by increasing the level of sex-hormone binding globulin and decreasing the levels of free estradiol (208). It was also found to inhibit cancer cell growth by targeting the phosphoinositide 3-kinase/Akt pathway (209). Studies have demonstrated that caffeine induces apoptosis in human neuroblastoma cells, in human A549 lung adenocarcinoma cells, and in mouse epidermal JB6 Cl 41 cells (210-212).

5.3.1.2 Breast cancer

The null findings regarding the association between coffee consumption and the risk of breast cancer found in paper 1 are in accordance with the meta-analyses by Jian et al., and Li et al., which included 37 and 26 studies, respectively (87, 88). In a recent meta-analysis of 13 prospective cohort studies, Lafranconi et al. concluded that the coffee intake was not associated with the risk of breast cancer overall, but also reported that consumption of four cups of coffee per day was associated with a 10% reduction of breast cancer in postmenopausal women (213). Similarly, no apparent association was found in prospective studies from Norway, United Kingdom, France, Netherlands, United States, and Sweden (85, 139, 214-221). Our findings support the results from the EPIC cohort in which total coffee consumption was not associated with the risk of breast cancer in pre- or postmenopausal women (222). However, the authors of the EPIC study suggest that the high caffeinated coffee intake may reduce the risk of breast cancer in postmenopausal women. Further, the results from the Swedish

Women's Lifestyle and Health study showed a 19% (95% CI 6%-20%) decrease in risk of breast cancer in women who reported drinking at least 5 cups of coffee per day compared to women who drank 1-2 cups/day (223).

We observed a borderline non-significant inverse association between high moderate coffee consumption (more than 3 up to 7 cups/day) and the risk of breast cancer, and a borderline non-significant test of linear trend across consumption categories. The association became significant after we have excluded breast cancer cases that were diagnosed during the first two years of follow-up, as part of the lag-analysis.

5.3.1.3 Colorectal cancer

A meta-analysis of 19 prospective cohort studies have shown that coffee intake was not associated with the risk of colorectal cancer (highest vs lowest consumption category meta-RR=0.98; 95% CI 0.90-1.06). The authors did find a significantly reduced risk of colon cancer for every 4 cups per day increase (meta-RR=0.93; 95% CI 0.88-0.99) (90). Akter et al. conducted a meta-analysis of observational studies conducted in Japan. They found a non-significant association in both genders after pooling the results from 5 cohort studies. Summary OR from seven case-control studies has shown that higher coffee intake was reducing the risk of colorectal cancer by 22% (95% CI 5%-35%, I^2=51.6%) (224).

Authors from the EPIC cohort concluded that coffee consumption was not likely to be associated with the risk of colorectal cancer (225), as did the authors that used the data from the National Cancer Institute - Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (226), the authors from the Singapore Chinese Health Study (227), the authors from the Miyagi Cohort Study (228), and the authors that used the data from the Women's Health Initiative Observational Study (229). Moreover, no association between coffee consumption of at least 10 cups of coffee per day and the risk of colorectal cancer was reported in the cohort of Finnish women (230). Studies from Sweden and the United States that used a similar method of updating information on coffee consumption, also found no association between high coffee consumption and the risk of colorectal cancer in women (231, 232). In a recent pooled analysis of 8 cohort studies from Japan, the authors found that coffee consumption was not associated with the risk of colorectal cancer in women, but reported a 20% (95% CI: 1%-36%) reduced risk of colon cancer in female women who reported drinking at least three cups of coffee per day (233). A meta-analyses of 19 prospective cohort studies found the coffee intake was significantly reducing the risk of colorectal cancer at ≥ 5 cups per day of coffee consumption in men and women combined (90). The results from the NIH-AARP Diet and Health Study have shown that compared to not drinking, consumption of at least 6 cups of caffeinated coffee per day was reducing the risk of colon cancer in women by 31% (95% CI 8%-55%) (234).

Even though we found an association between high moderate coffee consumption and colorectal cancer risk, an absence of significant associations in remaining coffee consumption categories, and no evidence of linear relationship across consumption categories support the findings from the abovementioned studies. Furthermore, coffee consumption was associated with neither colon nor rectal cancer in the separate analyses.

5.3.1.4 Ovarian cancer

The results from paper 1 regarding ovarian cancer are in line with those from the EPIC cohort. The same authors conducted a meta-analysis of 5 cohort studies and confirmed lack of evidence to support an association between coffee and tea consumption and risk of ovarian cancer (102). No significant association was also reported in the studies from Netherlands and Sweden (235, 236) and in a recent Mendelian randomization study (237). Silvera et al. used the data from the Canadian National Breast Screening Study to find a HR of 1.62 (95% CI 0.95-2.75) of developing ovarian cancer for the women who reported drinking more than 4 cups of coffee per day compared to coffee abstainers (238).

Our findings strengthen the evidence of no association between coffee consumption and the risk of ovarian cancer.

5.3.1.5 Lung cancer

In 2010, Tang et al. reported a positive association between coffee consumption and the risk of lung cancer in the meta-analysis that included 5 cohort and 8 case-control studies (highest vs. lowest quantile meta-RR=1.27; 95% CI 1.04 - 1.54, increase of two cups per day meta-RR=1.14; 95% CI 1.04–1.26) (99). Later, Wang et al. complemented the analyses and concluded that there is a linear dose-response relationship between coffee consumption and risk of lung cancer (239). In two recent meta-analyses of epidemiological studies, Xie et al. found a non-significant summary OR of 1.16 for women in the highest coffee consumption category (99), whereas Galarraga et al. concluded that the association between coffee consumption and lung cancer might be confounded by tobacco smoking, as they found no association in never smokers (100). Stensvold and Jacobsen reported a two-fold increased risk of lung cancer in Norwegian women that were consuming at least 7 cups of coffee per day compared to those who drank no more than 2 cups (85). In the study from United States, a non-significant higher risk of lung cancer in women was associated with the highest level of coffee intake (≥4 cups/day vs ≤1 cup/day HR=1.10; 95% CI 0.95-1.26). The authors of the study concluded that the observed positive association found in both genders combined is most likely due to an imperfect adjustment for smoking exposure (240). Finally, coffee consumption was associated with the increased risk of small cell lung carcinoma in the Japan Public Health Center-based Prospective Study (241).

A strong correlation between smoking habits and coffee consumption observed in paper 1 can be at least partially explained by the shared metabolic pathway between caffeine and nicotine, via the CYP1A2 gene (27, 242), which is the main caffeine-metabolizing enzyme (243). Sulem et al. conducted a meta-analysis of genome-wide association studies of coffee consumption and found sequence variants related to coffee consumption habits that were located between CYP1A1 and CYP1A2 and near the aryl hydrocarbon receptor, which regulates the expression of the CYP enzymes (243). As both caffeine and nicotine upregulate the CYP1A2 pathway (242, 244), active smokers would need more caffeine compared to non-smokers in order to feel the effect of it (240). Indeed, a recent Mendelian randomization study confirmed that heavier smoking causally increases coffee intake (174). Therefore, any imperfect adjustment for smoking exposure could result in positive associations between coffee consumption and lung cancer risk.

Residual confounding due to smoking is a probable reason of the observed association between coffee consumption and the risk of lung cancer in paper 1. In order to counter the effect of residual confounding, we performed the analysis in never smokers, and found no evidence of an association. However, a small number of lung cancer cases among never smokers limited our analysis, and wide confidence intervals indicated that the results, even though they were not statistically significant, were imprecise. Therefore, even though the results were not significant at 5% level, and that we did not observe a significant trend between coffee consumption and the risk of lung cancer among women that had never smoked, some caution is necessary when interpreting the results from this analysis.

Some biological effect of coffee compounds could also provide a background to the observed positive association between coffee consumption and lung cancer. In contrast to its anticarcinogenic properties, caffeine was also reported to inhibit DNA repair mechanisms (245, 246). A study by Muller et al. have shown that caffeine negatively effects both the speed of DNA repair, and the residual damage after exposing mammalian cells to radiation (247).

Recently, the role of dietary *acrylamide* in carcinogenesis has been investigated. IARC has classified acrylamide in group 2A of carcinogens, i.e. as probable carcinogen to humans. Acrylamide is a chemical used in many industrial processes, but is also found in food and cigarette smoke (248, 249). Coffee is one of the major sources of dietary acrylamide (250). A survey from United States has shown that its levels ranged from 45 to 374 ng/g in unbrewed coffee grounds, from 172 to 539 ng/g in instant coffee crystals, and from 6 to 16 ng/mL in brewed coffee (251). The authors of a study from Sweden reported that coffee contributes with about 39% of total dietary acrylamide intake in Swedish population (252). In a study by Mojska et al., the levels of acrylamide was found to be highest in coffee substitutes (818 microg/kg), followed by instant coffee (358 microg/kg), and roasted coffee (179 microg/kg). The authors, however, did not find significant differences in the acrylamide levels between Coffea arabica and Coffea robusta (253). The studies have shown that acrylamide can induce

47

DNA adduction and mutagenesis, tumorigenesis, and was also shown to have a genotoxic potential (254). However, in two recent comprehensive literature reviews of epidemiologic studies of dietary acrylamide intake and the risk of cancer, the authors concluded that there are no consistent evidence that dietary acrylamide is associated with increased cancer risk (255, 256).

5.3.2 Paper 2

5.3.2.1 Renal cell cancer

The results regarding the association between coffee intake and the risk of renal carcinoma found in paper 2 are in agreement with most previously published studies. In a recent meta-analyses of 22 observational studies, Wijarnpreecha et al. found no association between high coffee consumption and the risk of renal cell carcinoma in overall and gender-stratified analyses (257).
In the prospective study from Norway, Stensvold and Jacobsen found no association between coffee consumption and the risk of renal carcinoma (85). The same was found in two cohorts from United States - the Nurses' Health study (258), and the National Cancer Institute - Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (137), as well as in the The Million Women study from United Kingdom (259).

Contrary to these studies, the results from the VIP cohort, which included only 56 cases of renal cell carcinoma, have shown that a total coffee consumption of ≥4 cups/day was associated with 70% reduced risk of renal cell carcinoma (95% CI 21% - 89%) compared to coffee consumption of <1 cup/day. The analysis was, however, limited due to a low number of cases in the highest coffee consumption category (9 cases) and in the reference category (8 cases). No significant association was found for filtered and boiled coffee consumption (139).

5.3.2.2 Esophageal cancer

In the meta-analysis published in 2013, Zheng et al. concluded that coffee has a protective effect on esophageal cancer (260). The summary odds ratio of 16 observational studies for highest vs lowest/no coffee consumption category was 0.88 (95% CI: 0.76-1.01). Jacobsen et al. found no association between coffee consumption and the risk of esophageal cancer in a study that included only 22 cases (84). The study from Japan reported an inverse association between coffee consumption and the risk of oral cavity, pharyngeal, and esophageal cancers combined (157 cases; HR = 0.51; 95% CI 0.33-0.77) (261). The results from the EPIC cohort have shown no evidence of an association between tea and coffee consumption and esophageal cancer risk overall, although there were indications that increased coffee consumption was associated with decreased risk of esophageal squamous cell carcinoma among men (262). This is in line with the conclusions of Islami et al., who stated that there was little evidence of an association between coffee consumption and the risk of esophageal cancer

after summarizing the results from 22 observational studies (95). Finally, the Working Group of IARC stated that the available evidence suggested that even though the risk of esophageal cancer increased with the quantity of mate consumed, the trend was statistically significant only when high temperature mate was consumed, independent of the amount (83, 97).

Our results support the findings of the studies that concluded that coffee consumption does not affect the risk of esophageal cancer. The main issue with the analyses of coffee and esophageal cancer in paper 2 is that the analyses were statistically underpowered. Although the problem was less pronounced in the analysis of the entire sample, the issue became more evident in the gender-specific analyses and in the analyses stratified according to smoking status.

5.3.2.3 Bladder cancer

We did not observe significant association between coffee consumption and the risk of bladder cancer in men. This result contradicts the result from the 2015 meta-analysis (ref) in which positive association was reported in men (highest vs lowest coffee consumption category meta-OR=1.31; 95% CI 1.08-1.59). In both genders, the corresponding meta-OR was 1.33 (95% CI 1.19-1.48) with a moderate level of heterogeneity among 6 cohort and 34 case-control studies. On the other hand, positive associations among never smokers (meta-OR of 1.72 (95% CI: 1.25 to 2.35) are in agreement with our findings (86). In preceding meta-analysis, Zhou et al. concluded that "although data from case–control studies suggested that coffee was a risk factor for bladder cancer, there was no conclusive evidence on this association because of inconsistencies between case–control and cohort studies" (263).

The results from prospective cohort studies are partially in disagreement with our findings. The study from Netherlands found that the coffee was positively associated with the bladder cancer risk in men, and inversely associated in women (264). Kuarashi et al. found no association in both genders combined. However, they found that the coffee was significantly increasing the risk of bladder cancer in men who were never smokers (≥1 cup/day vs almost none HR = 2.48; 95% CI 0.88–7.05) (30). It should be noted that the cut-offs of coffee consumption categories used in this analysis were in discrepancy with the cut-offs in paper 2. A strong inverse relationship was observed in both genders, and in the analyses stratified according to smoking status in the paper by Sugiyama et al. However, none of the estimates were statistically significant, which could be the result of a small number of cancer cases in each gender and smoking status subgroups (265), a problem which was less pronounced in our analyses. Finally, in the large prospective cohort from the United States, coffee consumption was positively associated with bladder cancer risk (≥4 cups/d vs coffee abstainers HR=1.18; 95% CI 1.05-1.33). The association was additionally attenuated after adjustment for lifetime

smoking patterns (P trend = 0.16). The observed association was confined to men, and no such association was found in never smokers (266).

We did not have additional information on smoking measures such as number of cigarettes smoked per day, number of pack-years, and/or duration of smoking in years in the Swedish cohort and information on family history of bladder cancer was not available in neither of the two cohorts. However, as we did not observe any significant positive association between coffee consumption and the risk of bladder cancer in the analysis of the entire cohort, we believe that additional adjustment for aforementioned factors would not change our conclusions. Regarding the analysis of boiled coffee consumption and the risk of bladder cancer in women, we indeed found an increased risk for moderate coffee consumers. However, we believe that if residual confounding by smoking was present in the analysis, we would have observed the same positive association, if not stronger, for the heavy coffee consumers, when in fact we found a non-significant inverse association in that group.

Our conclusion further suggest that coffee consumption might affect the risk of bladder cancer in never smokers. The effect was also observed in the analyses of different coffee types, which is novel finding that requires further research. However, again it should be pointed out that the subgroup analyses were to some extent statistically underpowered, which demands caution in interpretation of the results.

Occupational exposure to polycyclic aromatic hydrocarbons was previously found to be associated with bladder cancer risk (267-270). Polycyclic aromatic hydrocarbons are also carcinogens formed by cigarette smoking and are activated by CYP1A2 and NAT2 liver enzymes, which production is stimulated by caffeine (28, 30). As discussed in 5.2.1.5, a shared metabolic pathway by nicotine and caffeine suggests that metabolism of caffeine might be faster in active smokers (27, 242). This provides a possible biological mechanism behind the potential carcinogenic effect of coffee in never smokers.

5.3.2.4 Pancreatic cancer

Two meta-analyses that were published during one year (2016) had conflicting results (106, 271). Nie et al. found that one additional cup of coffee per day was increasing the risk of pancreatic cancer by 1%, but found no association when comparing highest vs lowest coffee intake categories (meta-RR=0.99; 95% CI 0.81-1.21), with a moderate level of heterogeneity between the included studies (271). On the other hand, Ran et al. summarized the evidence of 20 cohort studies to find the overall RR for highest coffee consumption *vs* lowest coffee consumption of 0.75 (95% CI 0.63-0.86) and moderate level of heterogeneity (106).

Guertin et al. used data from the NIH-AARP Diet and Health cohort and reported no association between total, caffeinated, or decaffeinated coffee consumption and the risk of pancreatic cancer either

men or women (272). Similarly, no association was found in two studies from Norway, one from Finland, in the study of two prospective cohorts from the United States, and in the EPIC cohort (84, 85, 273-275). The pooled analysis of 14 cohort studies included in the Pooling Project of Prospective Studies of Diet and Cancer has shown no statistically significant associations between pancreatic cancer risk and intake of coffee (RR = 1.10; 95% CI, 0.81-1.48 comparing ≥900 to <0 g/d; 237g ≈ 8oz) (276).

Nilsson et al. included participants from the VIP cohort and found that the consumption of ≥4 cups/day of boiled coffee was associated with a 2.51-time (95% CI 1.15-5.50) increased risk of pancreatic cancer compared to consumption of >1 cup/day, with only 8 cases in the highest boiled coffee consumption group. However, they did not find evidence of an association for total or filtered coffee consumption (139). The authors of the study in Japan also concluded that coffee consumption has no substantial impact on pancreatic cancer risk.

The protective effect of filtered coffee on the risk of pancreatic cancer observed in our study was also found in never smokers but was not observed in men and women separately. In women, we observed borderline non-significant inverse associations in both coffee categories, whereas in men, the considerable effect size of 0.57 in the highest coffee consumption category was not statistically significant at 5% level. Similarly, the lack of statistical power hampered the analysis, as only 105 pancreatic cancer cases were available in men, contrary to 374 cases in women.

The difference in diet between consumers of boiled and filtered coffee types might give some insight in why the inverse association between coffee consumption and the risk of pancreatic cancer was found only for filtered coffee. Nilsson et al. have shown that boiled coffee consumers are more likely to have more traditional food habits, and are less adapted to a modern, more sedentary lifestyle compared to filtered coffee consumers (277). Therefore, we have conducted additional analyses in which we have additionally adjusted for the total energy intake and for red meat consumption. Our conclusions did not change after the additional adjustment in any of the outcomes.

Two recent meta-analyses have shown that increased coffee consumption has been inversely associated with a risk of type 2 diabetes (278, 279), which is an established risk factor for pancreatic cancer (280). In addition to anticarcinogenic properties of coffee compounds discussed in 5.2.1.1, Gururajanna et al. found that caffeine could induce apoptosis in human pancreatic adenocarcinoma cells (281). As the protective effect was found only for higher filtered coffee intake, anticancerogenic effect of coffee diterpenes, kahweol and cafestol seems unlikely, as concentration of these compounds in filtered coffee is very low (49-51).

5.3.2.5 Stomach cancer

Between 2014 and 2016, seven meta-analyses were conducted in order to summarize evidence on coffee consumption and the stomach/gastric cancer risk. Xie et al. pooled results from 12 cohort studies and concluded that coffee consumption was not associated with the gastric cancer risk (109). Seven months later, Shen et al. published the study in which they found a meta-RR of 1.24 (95% CI 1.03-1.49) for developing gastric cancer in the highest coffee consumption category, after combining the results from 8 studies (282). One month later, Liu et al. summarized 9 cohort studies and found that coffee consumption was indeed increasing the risk of gastric cancer but only of cardia sublocation (110). The same year in September, Zeng et al. found a RR of stomach cancer of 1.18 (95% CI 0.90-1.15) for the highest coffee consumption category after pooling the results from 15 cohort studies, and a RR of 1.07 (95% CI 0.95-1.21) for every 3-cup/day increase in total coffee consumption (112). October 2015: Li et al. published a meta-analysis of 13 cohort studies and concluded that coffee consumption was not associated with the risk of gastric cancer, although they found an increased risk in studies from the United States (111). Later that year, Deng et al. reported a significantly increased risk between gastric cardia cancer and coffee consumption (meta-RR = 1.50; 95% CI 1.09-2.07) (113). Finally, Xie et al. revisited the subject, and in an updated meta-analysis of 9 cohort and 13 case-control studies found that among the studies published over the last ten years, high coffee consumption was associated with decreased risk of gastric cancer (RR=0.88; 95% CI 0.77-1.00) (283).

Our findings support the conclusion from the EPIC study, in which no significant association was found between total coffee consumption and the risk of gastric cancer overall. However, in the same study, increment of 100 mL/day was increasing the risk of cardia cancer by 6% (95% CI 3%-11%) (284). Similarly, Larsson et al. found that an increase of 1 cup of coffee per day was associated with a 22% increased risk of stomach cancer (95% CI = 5%-42%) in the study of Swedish women (285). No association between coffee consumption and stomach cancer was found in two studies from Norway (84, 85). Similarly, Bidel et al. found that even coffee consumption of at least 10 cups of coffee per day did not affect the risk of gastric cancer (273). Finally, the results from the Singapore Chinese health study have shown that women who were daily coffee drinkers had RR of 0.63 (95% CI 0.46-0.87) for developing gastric cancer, compared to women who were coffee abstainers (286).

An increased risk of gastric cancer associated with high coffee consumption in never smokers warrant further investigation. Again, statistical power was one of the challenges, as only 98 cases were diagnosed among never smokers and could have been included in the analysis. Further, misclassification of smoking exposure might have contributed to the positive association that was found.

The observed differences between the results in paper 1 and the results from previously published studies on coffee and cancer could also be the result of different cut-off points of coffee consumption categories that were used. Indeed, only the studies from Finland had the highest category cut-off at the values that were higher than in paper 1 (≥10 cups/day; (230, 273). In rest of the studies, the highest coffee consumption category rarely exceeded 4 cups of coffee per day, which was deemed as high moderate coffee consumption in paper 1.

Moreover, differences between reference categories were also frequent. Most of the studies used coffee abstainers as their reference group, unlike in both papers 1 and 2 in which the reference were the women who reported drinking no more than 1 cup per day. In the NOWAC questionnaire, women could choose from the following answers regarding coffee intake: never/seldom, 1-6 cups/week, 1 cup/day, 2-3 cups/day, 4-5 cups/day, 6-7 cups/day, and ≥8 cups/day, for each brewing type. As none of the offered answers included "never" but rather "never" OR "seldom", there were no guarantees that a woman who had answered never/seldom was actually non-drinker of each coffee type. Moreover, the number of women who had answered never/seldom at baseline was only 6 315, compared to 17 044 women who were defined as "light consumers" in paper 1. Therefore, choosing the women who had answered never/seldom as a reference would have substantially limited the size of the group. Moreover, seldom drinking or abstaining from coffee is uncommon in Norway. Therefore, we believe that those women could differ from the women who reported drinking coffee more frequently, making them less appropriate as a reference group. However, using ≤1 cup/day may attenuate risk estimates in papers 1 and 2, as drinking 1 cup/day and being a never coffee drinker are different levels of exposure.

Finally, total coffee consumption in paper 1 was calculated as a sum of filtered, boiled, and instant coffee. As discussed in 5.1.1.2, we did not have information on consumption of espresso, cappuccino, café latte, macchiato, or decaffeinated coffee, and these types of coffee might have been included in the previously published studies. Further, if there was a difference in distribution of coffee species (C. arabica vs robusta) that were consumed among participants in different cohorts, this could add to the explanations of why the estimates were different in some studies, due to a different antioxidant capacity between the species.

5.3.3 Paper 3

From 2015 up until this day, five meta-analyses were conducted with the aim to summarize available evidence on association between coffee consumption and endometrial cancer risk. In the same period one new prospective cohort or case-control studies with same aim were published (1). However, the recent meta-analyses, other than the meta-analysis by Lafranconi et al. (93), did not perform optimal subgroup analyses according to important risk factors such as smoking or BMI. For example, the study

by Zhou et al. included only four studies to assess how BMI modified the coffee and endometrial cancer association, and did not conduct further analyses for overweight and obese women (92).

We conducted a dose-response meta-analysis of observational studies on coffee intake and endometrial cancer risk, including further detailed subgroup analyses according to established risk factors for endometrial cancer. We found that in both cohort and case-control studies, increased coffee consumption was associated with a lower risk of endometrial cancer. Dose-response meta-analyses revealed a 3% and 12% risk reduction for every additional cup/day increment based on the pooled results from cohort and case-control studies, respectively.

The results from Paper 3 are in agreement with the previous published meta-analyses (92, 93, 131, 201, 287-289) and the IARC Monograph evaluation (83). Yu et al. pooled the estimates from four cohort studies to find a meta-RR of 0.74 (95% CI 0.63-0.84) for the highest coffee intake category compared to lowest (201). Bravi et al. combined the results from seven case-control and two cohort studies (287). In their analyses they used method that was similar to our alternative approach and found an inverse association in coffee drinkers compared to nondrinkers (meta-RR 0.80; 95% CI: 0.68-0.94) and in heavy coffee drinkers compared to nondrinkers (meta-RR 0.64; 95% CI: 0.48-0.86). The dose-response analysis of case-control studies revealed 7% (95% CI: 4%-11%) lower risk of endometrial cancer for every additional cup of coffee. However, no significant dose-response was found for cohort studies (287). Je and Giovannucci used the results from ten case-control studies and six cohort studies and reported meta-RR for the highest vs lowest categories of coffee intake of 0.71 (95% CI: 0.62–0.81) after they combined the estimates from both study designs. For the case-control studies alone meta-OR was 0.69 (95% CI: 0.55–0.87) and meta-RR of 0.70 (95% CI: 0.61–0.80) was found for cohort studies. Similar to our results, the authors observed an inverse association across geographical regions. Finally, An increment of one cup per day of coffee intake was associated with 8% reduced risk of endometrial cancer (95% CI: 5%–10%) (288).

Yang et al. also utilized the results from both prospective and retrospective studies. Total of 7 cohort and 6 case-control studies from Europe (including two studies from Norway that were excluded in paper 3 (84, 85)) and North America were used to estimate meta-RR per additional coffee cup of 0.96 (95% CI 0.95-0.98) for cohort studies, and, similarly to our findings, a stronger association for case-control studies (meta-RR 0.91; 95% CI 0.87-0.95) (131). Zhou et al. conducted comprehensive meta-analyses of 13 cohort studies (92). The authors also included studies by Jacobsen et al., and Stensvold and Jacobsen; they did not include the results from part of the study by Merritt et al. (132), and the study by Hashibe et al., which was published later (137). As stated above, Zhou et al. used only four studies in the subgroup analyses of overweight/obese women compared to seven cohorts in the present review (92), and found that the women in the highest coffee consumption group that had BMI ≥ 25 had meta-RR of 0.57 (95% CI 0.46–0.71) of developing endometrial cancer compared to their

counterparts that were in the lowest coffee consumption category. Our more comprehensive subgroup analyses according to BMI status revealed that the significant effect of coffee consumption in women with BMI over 25 was driven by the effect in women with obesity, as no significant association was found in overweight women. The results from dose-response analyses using a linear model were similar to results from flexible spline models in our analyses (92). Further, Wang et al. found a similar protective effect after pooling the results from 12 cohort studies with meta-RR=0.88 (95% CI 0.85-0.92) for increment of 2 cups of coffee per day (289). Finally, the results from the meta-analysis by Lafranconi et al. in which the results from 12 cohort studies were included, were almost identical to the meta-RRs of cohort studies and corresponding subgroup analyses in paper 3 (93).

As previously mentioned, high coffee intake was found to reduce risk of type 2 diabetes (278, 279), which is also an independent risk factor for endometrial cancer (290-292). In addition to already mentioned benefits of kahweol, Cardenas et al. reported that coffee diterpene has inhibitory effects on tumor cell growth and survival of some types of breast cancer cells (293). Both caffeinated and decaffeinated coffee was found to decrease serum C-peptide concentrations, with the strongest effect observed in obese women (294). Some studies have shown that elevated levels of C-peptide were associated with an increased risk of endometrial cancer (295, 296). High coffee intake was also positively associated with increased serum levels of adiponectin (297, 298), a protein secreted by adipose tissue with antiinflammatory, antiatherogenic, proapoptotic, and antiproliferative properties (299). Based on the results from the recent meta-analyses, Li et al. suggested that adiponectin might be a promising tool for the prevention of endometrial cancer in postmenopausal women (300). Finally, elevated levels of circulating sex-hormone-binding globulin reduce the concentrations of bioavailable sex-steroid hormones, which again were positively associated with a risk of endometrial cancer in high concentrations (301). Caffeine was suggested to increase levels of circulating sex-hormone-binding globulin, with the effect being more pronounced in obese women (208, 302-304).

6 Conclusion

1. Intake from 4 to 7 cups of coffee per day might reduce overall risk of cancer.
2. Coffee consumption even in high quantities was not affecting the risk of ovarian and breast cancer. Even though there were some indications that moderate-high coffee consumption might reduce the risk of colorectal cancer, the absence of dose-response relationship implied no association between coffee intake and colorectal cancer risk.
3. The positive association between heavy coffee consumption (more than 7 cups/day) and the risk of lung cancer is most likely confounded by smoking exposure, as no significant association was found in never smokers.
4. The results from the meta-analysis strengthen the evidence of a protective effect of coffee consumption on the risk of endometrial cancer and further suggests that increased coffee intake might be particularly beneficial for women with obesity.
5. Increased consumption of filtered coffee was associated with a lower risk of pancreatic cancer.
6. In both men and women, filtered and total coffee consumption were not associated with the risk of bladder, esophageal, kidney, and stomach cancer. Some evidence of a positive association between boiled coffee consumption and the risk of bladder cancer was found only in women, with, however, no evidence of dose-response relationship between boiled coffee intake and bladder cancer risk.
7. The positive association between boiled coffee consumption and risk of stomach cancer, and between filtered, boiled, and total coffee consumption and risk of bladder cancer was found in never smokers. These findings should be interpreted with caution, as the analyses were hampered by the small number of cases.

7 Further perspectives

1. More prospective studies are needed to clarify the association between coffee and breast and colorectal cancer risk.

2. The future studies that aim to explore the relationship between coffee consumption and the risk of lung cancer should have data with extensive information on smoking exposure such as smoking duration, number of cigarettes, long-term exposure to cigarette smoke, time since quitting, type of tobacco, etc… These studies should involve multiple cohorts that would provide sufficient number of lung cancer cases among never smokers in order to provide reasonably precise estimates of coffee intake in this sub-population.

3. Analysis of different coffee types (filtered, boiled, instant) are warranted for the most frequently diagnosed cancer sites.

4. The studies of coffee consumption and endometrial cancer should aim to clarify the effect of coffee in different subgroups, mainly in overweight/obese women.

5. The future studies on rare cancer sites such as esophageal, bladder, and stomach are warranted and should aim to pool several cohorts in order to have sufficient statistical power. This also holds true if the aim of the studies is to explore the association of coffee consumption on the risk of rare cancers within different subgroups.

6. More studies are needed that would aim to elucidate the biological mechanisms behind a positive association between high coffee intake and risk of bladder cancer in never smokers.

References

1. Feil R. Coffea. Genus, Species, Varieties [Internet]. March 2011. [cited 14 Feb 2018]. Available from: https://www.scribd.com/document/61317434/Coffea-Genus-species-varieties?ad_group=725X1370566Xc44b993114eea1aac72d1c994ee04f4e&campaign=SkimbitLtd&keyword=660149026&medium=affiliate&source=hp_affiliate
2. Ludwig IA, Clifford MN, Lean MEJ, Ashihara H, Crozier A. Coffee: biochemistry and potential impact on health. Food Funct. 2014;5(8):1695-717.
3. Patay EB, Bencsik T, Papp N. Phytochemical overview and medicinal importance of Coffea species from the past until now. Asian Pac J Trop Med. 2016;9(12):1127-35.
4. Tesfaye K, Govers K, Bekele E, Borsch T. ISSR fingerprinting of Coffea arabica throughout Ethiopia reveals high variability in wild populations and distinguishes them from landraces. Plant Syst Evol. 2014;300(5):881-97.
5. Mazzafera P, Crozier A, Magalhaes AC. Caffeine Metabolism in Coffea-Arabica and Other Species of Coffee. Phytochemistry. 1991;30(12):3913-6.
6. Wolf A, Bray GA, Popkin BM. A short history of beverages and how our body treats them. Obes Rev. 2008;9(2):151-64.
7. Kipple KF. Ornelas KC. (Editors). The Cambridge World History of Food (2-Volume Set). 1st Ed. Cambridge, UK: Cambridge University Press. March 2008. https://doi.org/10.1017/CHOL9780521402149
8. Kolbu C. A History of Coffee in Norway, Part One [Internet]. Nordic Coffee Culture. 2017. [cited 14 Feb 2018]. Available from: http://nordiccoffeeculture.com/a-history-of-coffee-in-norway-part-one/
9. Kolbu C. A History of Coffee in Norway, Part Two [Internet]. Nordic Coffee Culture. 2017. [cited 14 Feb 2018]. Available from: http://nordiccoffeeculture.com/a-history-of-coffee-in-norway-part-two/
10. Wyndham FM. Wild Life on the Fjelds of Norway. [With chromo-lithographs and maps.]. London, UK: British Library, Historical Print Editions. January 2011.
11. Kolbu C. A History of Coffee in Norway, Part Three [Internet]. Nordic Coffee Culture. 2017. [cited 14 Feb 2018]. Available from: http://nordiccoffeeculture.com/a-history-of-coffee-in-norway-part-three/
12. Kolbu C. A History of Coffee in Norway, Part Five [Internet]. Nordic Coffee Culture. 2017. [cited 14 Feb 2018]. Available from: http://nordiccoffeeculture.com/a-history-of-coffee-in-norway-part-five/
13. International Coffee Council. Trends in coffee consumption in selected importing countries. 2015. Available from: http://www.ico.org/documents/icc-109-8e-trends-consumption.pdf
14. Grydeland B. Kaffe og Kolesterol [Internet]. Norsk Kaffeinformasjon. December 2017. [cited 16 Feb 2018]. [Norwegian]. Available from: http://kaffe.no/kaffe-og-kolesterol/
15. Statistisk Sentralbyrå. Statistics Norway. Uten Kafe Stopper Norge [Internet]. July 2011. [cited 16 Feb 2018]. [Norwegian]. Available from: https://www.ssb.no/utenriksokonomi/artikler-og-publikasjoner/uten-kaffe-stopper-norge
16. Statista. Per capita consumption of roasted coffee in Sweden from 2006 to 2016 (in kilograms) [Intenet]. Statista. 2018. [cited 13 Jun 2018]. Available from: https://www.statista.com/statistics/560194/per-capita-consumption-of-coffee-in-sweden/
17. Nieber K. The Impact of Coffee on Health. Planta Med. 2017;83(16):1256-63.
18. Nuhu AA. Bioactive micronutrients in coffee: recent analytical approaches for characterization and quantification. ISRN Nutr. 2014;2014:384230.
19. Heckman MA, Weil J, Gonzalez de Mejia E. Caffeine (1, 3, 7-trimethylxanthine) in foods: a comprehensive review on consumption, functionality, safety, and regulatory matters. J Food Sci. 2010;75(3):R77-87.
20. Fox GP, Wu A, Yiran L, Force L. Variation in caffeine concentration in single coffee beans. J Agric Food Chem. 2013;61(45):10772-8.
21. Liang N, Kitts DD. Antioxidant property of coffee components: assessment of methods that define mechanisms of action. Molecules. 2014;19(11):19180-208.

22.   Tfouni SAV, Carreiro LB, Teles CRA, Furlani RPZ, Cipolli KMVAB, Camargo MCR. Caffeine and chlorogenic acids intake from coffee brew: influence of roasting degree and brewing procedure. Int J Food Sci Tech. 2014;49(3):747-52.

23.   National Center for Biotechnology Information. Pubchem. Open chemistry database. Caffeine [image on the internet]. Bethesda (MD): US National Library of Medicine, National Center for Biotechnology Information. 2004 [updated 2018 June 23; cited 2018 June 25]. [Figure]. Chemical structure of caffeine. Available from:
https://pubchem.ncbi.nlm.nih.gov/image/imgsrv.fcgi?cid=2519&t=l

24.   Fredholm BB, Battig K, Holmen J, Nehlig A, Zvartau EE. Actions of caffeine in the brain with special reference to factors that contribute to its widespread use. Pharmacol Rev. 1999;51(1):83-133.

25.   Institute of Medicine. Caffeine for the Sustainment of Mental Task Performance: Formulations for Military Operations. Washington, DC: The National Academies Press. 2001. https://doi.org/10.17226/10219.

26.   Thorn CF, Aklillu E, McDonagh EM, Klein TE, Altman RB. PharmGKB summary: caffeine pathway. Pharmacogenet Genom. 2012;22(5):389-95.

27.   Gu L, Gonzalez FJ, Kalow W, Tang BK. Biotransformation of caffeine, paraxanthine, theobromine and theophylline by cDNA-expressed human CYP1A2 and CYP2E1. Pharmacogenetics. 1992;2(2):73-7.

28.   Porta M, Vioque J, Ayude D, Alguacil J, Jariod M, Ruiz L, et al. Coffee drinking: the rationale for treating it as a potential effect modifier of carcinogenic exposures. Eur J Epidemiol. 2003;18(4):289-98.

29.   Blum M, Demierre A, Grant DM, Heim M, Meyer UA. Molecular mechanism of slow acetylation of drugs and carcinogens in humans. Proc Natl Acad Sci U S A. 1991;88(12):5237-41.

30.   Kurahashi N, Inoue M, Iwasaki M, Sasazuki S, Tsugane S, Japan Public Health Center Study G. Coffee, green tea, and caffeine consumption and subsequent risk of bladder cancer in relation to smoking status: a prospective study in Japan. Cancer Sci. 2009;100(2):294-91.

31.   Wittayalertpanya S, Hinsui Y, Lawanprasert S. Paraxanthine/caffeine ratio: as an index for CYP1A2 activity in polycyclic aromatic hydrocarbons exposed subjects. J Med Assoc Thai. 2003;86 Suppl 2:S310-7.

32.   Laurence G, Wallman K, Guelfi K. Effects of caffeine on time trial performance in sedentary men. J Sports Sci. 2012;30(12):1235-40.

33.   Schwarzschild MA, Xu K, Oztas E, Petzer JP, Castagnoli K, Castagnoli N, Jr., et al. Neuroprotection by caffeine and more specific A2A receptor antagonists in animal models of Parkinson's disease. Neurology. 2003;61(11 Suppl 6):S55-61.

34.   Prediger RD. Effects of caffeine in Parkinson's disease: from neuroprotection to the management of motor and non-motor symptoms. J Alzheimers Dis. 2010;20 Suppl 1:S205-20.

35.   Azam S, Hadi N, Khan NU, Hadi SM. Antioxidant and prooxidant properties of caffeine, theobromine and xanthine. Med Sci Monit. 2003;9(9):BR325-30.

36.   Jeszka-Skowron M, Sentkowska A, Pyrzynska K, De Pena MP. Chlorogenic acids, caffeine content and antioxidant properties of green coffee extracts: influence of green coffee bean preparation. Eur Food Res Technol. 2016;242(8):1403-9.

37.   Rogers PJ, Heatherley SV, Mullings EL, Smith JE. Faster but not smarter: effects of caffeine and caffeine withdrawal on alertness and performance. Psychopharmacology (Berl). 2013;226(2):229-40.

38.   Smith A. Effects of caffeine on human behavior. Food Chem Toxicol. 2002;40(9):1243-55.

39.   Cavin C, Holzhaeuser D, Scharf G, Constable A, Huber WW, Schilter B. Cafestol and kahweol, two coffee specific diterpenes with anticarcinogenic activity. Food Chem Toxicol. 2002;40(8):1155-63.

40.   Cardenas C, Quesada AR, Medina MA. Anti-angiogenic and anti-inflammatory properties of kahweol, a coffee diterpene. PLoS One. 2011;6(8):e23407.

41.   Oh JH, Lee JT, Yang ES, Chang JS, Lee DS, Kim SH, et al. The coffee diterpene kahweol induces apoptosis in human leukemia U937 cells through down-regulation of Akt phosphorylation and activation of JNK. Apoptosis. 2009;14(11):1378-86.

42. Majer BJ, Hofer E, Cavin C, Lhoste E, Uhl M, Glatt HR, et al. Coffee diterpenes prevent the genotoxic effects of 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP) and N-nitrosodimethylamine in a human derived liver cell line (HepG2). Food Chem Toxicol. 2005;43(3):433-41.

43. Higgins LG, Cavin C, Itoh K, Yamamoto M, Hayes JD. Induction of cancer chemopreventive enzymes by coffee is mediated by transcription factor Nrf2. Evidence that the coffee-specific diterpenes cafestol and kahweol confer protection against acrolein. Toxicol Appl Pharmacol. 2008;226(3):328-37.

44. Lee KA, Chae JI, Shim JH. Natural diterpenes from coffee, cafestol and kahweol induce apoptosis through regulation of specificity protein 1 expression in human malignant pleural mesothelioma. J Biomed Sci. 2012;19:60.

45. Thelle DS, Arnesen E, Forde OH. The Tromso heart study. Does coffee raise serum cholesterol? N Engl J Med. 1983;308(24):1454-7.

46. Urgert R, Katan MB. The cholesterol-raising factor from coffee beans. Annu Rev Nutr. 1997;17:305-24.

47. Rustan AC, Halvorsen B, Huggett AC, Ranheim T, Drevon CA. Effect of coffee lipids (cafestol and kahweol) on regulation of cholesterol metabolism in HepG2 cells. Arterioscler Thromb Vasc Biol. 1997;17(10):2140-9.

48. Rustan AC, Halvorsen B, Ranheim T, Drevon CA. Cafestol (a coffee lipid) decreases uptake of low-density lipoprotein (LDL) in human skin fibroblasts and liver cells. Ann N Y Acad Sci. 1997;827:158-62.

49. Moeenfard M, Silva JA, Borges N, Santos A, Alves A. Quantification of Diterpenes and Their Palmitate Esters in Coffee Brews by HPLC-DAD. Int J Food Prop. 2015;18(10):2284-99.

50. Parras P, Martinez-Tome M, Jimenez AM, Murcia MA. Antioxidant capacity of coffees of several origins brewed following three different procedures. Food Chem. 2007;102(3):582-92.

51. Urgert R, Vanderweg G, Kosmeijerschuil TG, Vandebovenkamp P, Hovenier R, Katan MB. Levels of the Cholesterol-Elevating Diterpenes Cafestol and Kahweol in Various Coffee Brews. J Agr Food Chem. 1995;43(8):2167-72.

52. Rendon MY, Dos Santos Scholz MB, Bragagnolo N. Is cafestol retained on the paper filter in the preparation of filter coffee? Food Res Int. 2017;100(Pt 1):798-803.

53. van Dusseldorp M, Katan MB, van Vliet T, Demacker PN, Stalenhoef AF. Cholesterol-raising factor from boiled coffee does not pass a paper filter. Arterioscler Thromb. 1991;11(3):586-93.

54. National Center for Biotechnology Information. Pubchem. Open chemistry database. Cafestol [image on the internet]. Bethesda (MD): US National Library of Medicine, National Center for Biotechnology Information. 2005 [updated 2018 June 23; cited 2018 June 25]. [Figure]. Chemical structure of cafestol. Available from:
https://pubchem.ncbi.nlm.nih.gov/image/imgsrv.fcgi?cid=108052&t=l

55. National Center for Biotechnology Information. Pubchem. Open chemistry database. Kahweol [image on the internet]. Bethesda (MD): US National Library of Medicine, National Center for Biotechnology Information. 2005 [updated 2018 June 23; cited 2018 June 25]. [Figure]. Chemical structure of Kahweol. Available from:
https://pubchem.ncbi.nlm.nih.gov/image/imgsrv.fcgi?cid=114778&t=l

56. Narita Y, Inouye K. Degradation kinetics of chlorogenic acid at various pH values and effects of ascorbic acid and epigallocatechin gallate on its stability under alkaline conditions. J Agric Food Chem. 2013;61(4):966-72.

57. Clifford MN. Chlorogenic acids and other cinnamates - nature, occurrence, dietary burden, absorption and metabolism. J Sci Food Agr. 2000;80(7):1033-43.

58. Jeon JS, Kim HT, Jeong IH, Hong SR, Oh MS, Park KH, et al. Determination of chlorogenic acids and caffeine in homemade brewed coffee prepared under various conditions. J Chromatogr B. 2017;1064:115-23.

59. Zang LY, Cosma G, Gardner H, Castranova V, Vallyathan V. Effect of chlorogenic acid on hydroxyl radical. Mol Cell Biochem. 2003;247(1-2):205-10.

60. Farah A. Donangelo CM. Phenolic compounds in coffee. Braz. J. Plant Physiol. vol.18 no.1. Jan/Mar 2006. http://dx.doi.org/10.1590/S1677-04202006000100003.

61.   Richelle M, Tavazzi I, Offord E. Comparison of the antioxidant activity of commonly consumed polyphenolic beverages (coffee, cocoa, and tea) prepared per cup serving. J Agric Food Chem. 2001;49(7):3438-42.
62.   Shearer J, Farah A, de Paulis T, Bracy DP, Pencek RR, Graham TE, et al. Quinides of roasted coffee enhance insulin action in conscious rats. J Nutr. 2003;133(11):3529-32.
63.   Rawel HM, Kulling SE. Nutritional contribution of coffee, cacao and tea phenolics to human health. J Verbrauch Lebensm. 2007;2(4):399-406.
64.   Renehan AG, Roberts DL, Dive C. Obesity and cancer: pathophysiological and biological mechanisms. Arch Physiol Biochem. 2008;114(1):71-83.
65.   Bassoli BK, Cassolla P, Borba-Murad GR, Constantin J, Salgueiro-Pagadigorria CL, Bazotte RB, et al. Chlorogenic acid reduces the plasma glucose peak in the oral glucose tolerance test: effects on hepatic glucose release and glycaemia. Cell Biochem Funct. 2008;26(3):320-8.
66.   Arcidiacono B, Iiritano S, Nocera A, Possidente K, Nevolo MT, Ventura V, et al. Insulin resistance and cancer risk: an overview of the pathogenetic mechanisms. Exp Diabetes Res. 2012;2012:789174.
67.   Djiogue S, Nwabo Kamdje AH, Vecchio L, Kipanyula MJ, Farahna M, Aldebasi Y, et al. Insulin resistance and cancer: the role of insulin and IGFs. Endocr Relat Cancer. 2013;20(1):R1-R17.
68.   Perrone D, Farah A, Donangelo CM, de Paulis T, Martin PR. Comprehensive analysis of major and minor chlorogenic acids and lactones in economically relevant Brazilian coffee cultivars. Food Chem. 2008;106(2):859-67.
69.   Jeszka-Skowron M, Stanisz E, De Pena MP. Relationship between antioxidant capacity, chlorogenic acids and elemental composition of green coffee. Lwt-Food Sci Technol. 2016;73:243-50.
70.   Zanin RC, Corso MP, Kitzberger CSG, Scholz MBD, Benassi MD. Good cup quality roasted coffees show wide variation in chlorogenic acids content. Lwt-Food Sci Technol. 2016;74:480-3.
71.   National Center for Biotechnology Information. Pubchem. Open chemistry database. Chlorogenic acid [image on the internet]. Bethesda (MD): US National Library of Medicine, National Center for Biotechnology Information. 2004 [updated 2018 June 23; cited 2018 June 25]. [Figure]. Chemical structure of chlorogenic acid. Available from: https://pubchem.ncbi.nlm.nih.gov/image/imgsrv.fcgi?cid=1794427&t=l
72.   Borrelli RC, Visconti A, Mennella C, Anese M, Fogliano V. Chemical characterization and antioxidant properties of coffee melanoidins. J Agr Food Chem. 2002;50(22):6527-33.
73.   Gniechwitz D, Reichardt N, Ralph J, Blaut M, Steinhart H, Bunzel M. Isolation and characterisation of a coffee melanoidin fraction. J Sci Food Agr. 2008;88(12):2153-60.
74.   Moreira ASP, Nunes FM, Domingues MR, Coimbra MA. Coffee melanoidins: structures, mechanisms of formation and potential health impacts. Food Funct. 2012;3(9):903-15.
75.   Daglia M, Racchi M, Papetti A, Lanni C, Govoni S, Gazzani G. In vitro and ex vivo antihydroxyl radical activity of green and roasted coffee. J Agr Food Chem. 2004;52(6):1700-4.
76.   Liu YZ, Kitts DD. Confirmation that the Maillard reaction is the principle contributor to the antioxidant capacity of coffee brews. Food Research International. 2011;44(8):2418-24.
77.   Cammerer B, Kroh LW. Antioxidant activity of coffee brews. Eur Food Res Technol. 2006;223(4):469-74.
78.   Goya L, Delgado-Andrade C, Rufian-Henares JA, Bravo L, Morales FJ. Effect of coffee Melanoidin on human hepatoma HepG2 cells. Protection against oxidative stress induced by tert-butylhydroperoxide. Mol Nutr Food Res. 2007;51(5):536-45.
79.   Vitaglione P, Morisco F, Mazzone G, Amoruso DC, Ribecco MT, Romano A, et al. Coffee Reduces Liver Damage in a Rat Model of Steatohepatitis: The Underlying Mechanisms and the Role of Polyphenols and Melanoidins. Hepatology. 2010;52(5):1652-61.
80.   Cancer Registry of Norway. Cancer in Norway 2016 - Cancer incidence, mortality, survival and prevalence in Norway. Oslo: Cancer Registry of Norway, 2017.
81.   World Cancer Research Fund/American Institute for Cancer Research. Food, nutrition, physical activity and the Prevention of Cancer: a Global Perspective. Washington, DC: AICR, 2017. Available from: https://www.wcrf.org/sites/default/files/english.pdf
82.   Socialstyrelsen. Statistics on Cancer Incidence 2016 [Intenet]. Socialstyrelsen. 2017. [cited 1 May 2018]. Available from: https://www.socialstyrelsen.se/SiteCollectionDocuments/2017-12-30-tabeller.xls

83.   Loomis D, Guyton KZ, Grosse Y, Lauby-Secretan B, El Ghissassi F, Bouvard V, et al. Carcinogenicity of drinking coffee, mate, and very hot beverages. Lancet Oncol. 2016;17(7):877-8.
84.   Jacobsen BK, Bjelke E, Kvale G, Heuch I. Coffee drinking, mortality, and cancer incidence: results from a Norwegian prospective study. J Natl Cancer Inst. 1986;76(5):823-31.
85.   Stensvold I, Jacobsen BK. Coffee and cancer: a prospective study of 43,000 Norwegian men and women. Cancer Causes Control. 1994;5(5):401-8.
86.   Wu W, Tong Y, Zhao Q, Yu G, Wei X, Lu Q. Coffee consumption and bladder cancer: a meta-analysis of observational studies. Sci Rep. 2015;5:9051.
87.   Jiang W, Wu Y, Jiang X. Coffee and caffeine intake and breast cancer risk: an updated dose-response meta-analysis of 37 published studies. Gynecol Oncol. 2013;129(3):620-9.
88.   Li XJ, Ren ZJ, Qin JW, Zhao JH, Tang JH, Ji MH, et al. Coffee consumption and risk of breast cancer: an up-to-date meta-analysis. PLoS One. 2013;8(1):e52681.
89.   World Cancer Research Fund/American Institute for Cancer Research. Continuous Update Project Expert Report 2018. Diet, nutrition, physical activity and breast cancer. Available from: dietandcancerreport.org.
90.   Gan Y, Wu J, Zhang S, Li L, Cao S, Mkandawire N, et al. Association of coffee consumption with risk of colorectal cancer: a meta-analysis of prospective cohort studies. Oncotarget. 2017;8(12):18699-711.
91.   World Cancer Research Fund/American Institute for Cancer Research. Continuous Update Project Expert Report 2018. Diet, nutrition, physical activity and colorectal cancer. Available from: dietandcancerreport.org
92.   Zhou Q, Luo ML, Li H, Li M, Zhou JG. Coffee consumption and risk of endometrial cancer: a dose-response meta-analysis of prospective cohort studies. Sci Rep. 2015;5:13410.
93.   Lafranconi A, Micek A, Galvano F, Rossetti S, Del Pup L, Berretta M, et al. Coffee Decreases the Risk of Endometrial Cancer: A Dose-Response Meta-Analysis of Prospective Cohort Studies. Nutrients. 2017;9(11).
94.   World Cancer Research Fund/American Institute for Cancer Research. Continuous Update Project Expert Report 2018. Diet, nutrition, physical activity and endometrial cancer. Available from: dietandcancerreport.org
95.   Islami F, Boffetta P, Ren JS, Pedoeim L, Khatib D, Kamangar F. High-temperature beverages and foods and esophageal cancer risk--a systematic review. Int J Cancer. 2009;125(3):491-524.
96.   World Cancer Research Fund/American Institute for Cancer Research. Continuous Update Project Expert Report 2016. Diet, nutrition, physical activity and oesophageal cancer. Available from: dietandcancerreport.org
97.   Lubin JH, De Stefani E, Abnet CC, Acosta G, Boffetta P, Victora C, et al. Mate drinking and esophageal squamous cell carcinoma in South America: pooled results from two large multicenter case-control studies. Cancer Epidemiol Biomarkers Prev. 2014;23(1):107-16.
98.   Castellsague X, Munoz N, De Stefani E, Victora CG, Castelletto R, Rolon PA. Influence of mate drinking, hot beverages and diet on esophageal cancer risk in South America. Int J Cancer. 2000;88(4):658-64.
99.   Xie Y, Qin J, Nan G, Huang S, Wang Z, Su Y. Coffee consumption and the risk of lung cancer: an updated meta-analysis of epidemiological studies. Eur J Clin Nutr. 2016;70(2):199-206.
100.   Galarraga V, Boffetta P. Coffee Drinking and Risk of Lung Cancer-A Meta-Analysis. Cancer Epidemiol Biomarkers Prev. 2016;25(6):951-7.
101.   World Cancer Research Fund/American Institute for Cancer Research. Continuous Update Project Expert Report 2018. Diet, nutrition, physical activity and lung cancer. Available from: dietandcancerreport.org
102.   Braem MG, Onland-Moret NC, Schouten LJ, Tjonneland A, Hansen L, Dahm CC, et al. Coffee and tea consumption and the risk of ovarian cancer: a prospective cohort study and updated meta-analysis. Am J Clin Nutr. 2012;95(5):1172-81.
103.   Poole R, Kennedy OJ, Roderick P, Fallowfield JA, Hayes PC, Parkes J. Coffee consumption and health: umbrella review of meta-analyses of multiple health outcomes. BMJ. 2017;359:j5024.

104.   World Cancer Research Fund/American Institute for Cancer Research. Continuous Update Project Expert Report 2018. Diet, nutrition, physical activity and ovarian cancer. Available from: dietandcancerreport.org

105.   Turati F, Galeone C, Edefonti V, Ferraroni M, Lagiou P, La Vecchia C, et al. A meta-analysis of coffee consumption and pancreatic cancer. Ann Oncol. 2012;23(2):311-8.

106.   Ran HQ, Wang JZ, Sun CQ. Coffee Consumption and Pancreatic Cancer Risk: An Update Meta-analysis of Cohort Studies. Pak J Med Sci. 2016;32(1):253-9.

107.   World Cancer Research Fund/American Institute for Cancer Research. Continuous Update Project Expert Report 2018. Diet, nutrition, physical activity and pancreatic cancer. Available from: dietandcancerreport.org

108.   World Cancer Research Fund/American Institute for Cancer Research. Continuous Update Project Expert Report 2018. Diet, nutrition, physical activity and kidney cancer. Available from: dietandcancerreport.org

109.   Xie Y, Huang S, He T, Su Y. Coffee consumption and risk of gastric cancer: an updated meta-analysis. Asia Pac J Clin Nutr. 2016;25(3):578-88.

110.   Liu H, Hua Y, Zheng X, Shen Z, Luo H, Tao X, et al. Effect of coffee consumption on the risk of gastric cancer: a systematic review and meta-analysis of prospective cohort studies. PLoS One. 2015;10(5):e0128501.

111.   Li L, Gan Y, Wu C, Qu X, Sun G, Lu Z. Coffee consumption and the risk of gastric cancer: a meta-analysis of prospective cohort studies. BMC Cancer. 2015;15:733.

112.   Zeng SB, Weng H, Zhou M, Duan XL, Shen XF, Zeng XT. Long-Term Coffee Consumption and Risk of Gastric Cancer: A PRISMA-Compliant Dose-Response Meta-Analysis of Prospective Cohort Studies. Medicine (Baltimore). 2015;94(38):e1640.

113.   Deng W, Yang H, Wang J, Cai J, Bai Z, Song J, et al. Coffee consumption and the risk of incident gastric cancer--A meta-analysis of prospective cohort studies. Nutr Cancer. 2016;68(1):40-7.

114.   World Cancer Research Fund/American Institute for Cancer Research. Continuous Update Project Expert Report 2016. Diet, nutrition, physical activity and stomach cancer. Available from: dietandcancerreport.org

115.   Lund E, Dumeaux V, Braaten T, Hjartaker A, Engeset D, Skeie G, et al. Cohort profile: The Norwegian Women and Cancer Study--NOWAC--Kvinner og kreft. Int J Epidemiol. 2008;37(1):36-41.

116.   Tognon G, Nilsson LM, Shungin D, Lissner L, Jansson JH, Renstrom F, et al. Nonfermented milk and other dairy products: associations with all-cause mortality. Am J Clin Nutr. 2017;105(6):1502-11.

117.   Stegmayr B, Lundberg V, Asplund K. The events registration and survey procedures in the Northern Sweden MONICA Project. Scand J Public Health Suppl. 2003;61:9-17.

118.   Harrell FE. Regression Modeling Strategies with Applications to Linear Models, Logistic Regression and Survival Analysis, Jun, Springer‐Verlag, New York, 2001.

119.   Sterne JAC, White IR, Carlin JB, Spratt M, Royston P, Kenward MG, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. Bmj-Brit Med J. 2009;339.

120.   White IR, Royston P. Imputing missing covariate values for the Cox model. Stat Med. 2009;28(15):1982-98.

121.   Marshall A, Altman DG, Holder RL, Royston P. Combining estimates of interest in prognostic modelling studies after multiple imputation: current practice and guidelines. Bmc Med Res Methodol. 2009;9:57.

122.   Rubin DB. Multiple imputation after 18+ years. J Am Stat Assoc. 1996;91(434):473-89.

123.   Carlin JB. Li N. Greenwood P. Coffey C. Tools for analyzing multiple imputed datasets. Stata Journal, 2003, vol. 3, issue 3, 226-244.

124.   Dersimonian R, Laird N. Metaanalysis in Clinical-Trials. Control Clin Trials. 1986;7(3):177-88.

125.   Greenland S, Longnecker MP. Methods for trend estimation from summarized dose-response data, with applications to meta-analysis. Am J Epidemiol. 1992;135(11):1301-9.

126.   Orsini N, Li R, Wolk A, Khudyakov P, Spiegelman D. Meta-analysis for linear and nonlinear dose-response relations: examples, an evaluation of approximations, and software. Am J Epidemiol. 2012;175(1):66-73.

127.   Orsini N, Bellocco R, Greenland S. Generalized least squares for trend estimation of summarized dose-response data. Stata J. 2006;6(1):40-57.

128.   Orsini N. Multivariate dose-response meta-analysis: an update on glst [Internet]. 2013. [cited 12 May 2018]. Available from: http://www.stata.com/meeting/nordic-and-baltic13/abstracts/materials/se13_orsini.pdf

129.   Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. Brit Med J. 2003;327(7414):557-60.

130.   Peters JL, Sutton AJ, Jones DR, Abrams KR, Rushton L. Comparison of two methods to detect publication bias in meta-analysis. Jama-J Am Med Assoc. 2006;295(6):676-80.

131.   Yang TO, Crowe F, Cairns BJ, Reeves GK, Beral V. Tea and coffee and risk of endometrial cancer: cohort study and meta-analysis. Am J Clin Nutr. 2015;101(3):570-8.

132.   Merritt MA, Tzoulaki I, Tworoger SS, De Vivo I, Hankinson SE, Fernandes J, et al. Investigation of Dietary Factors and Endometrial Cancer Risk Using a Nutrient-wide Association Study Approach in the EPIC and Nurses' Health Study (NHS) and NHSII. Cancer Epidem Biomar. 2015;24(2):466-71.

133.   Je YJ, Hankinson SE, Tworoger SS, DeVivo I, Giovannucci E. A Prospective Cohort Study of Coffee Consumption and Risk of Endometrial Cancer over a 26-Year Follow-Up. Cancer Epidem Biomar. 2011;20(12):2487-95.

134.   Gavrilyuk O, Braaten T, Skeie G, Weiderpass E, Dumeaux V, Lund E. High coffee consumption and different brewing methods in relation to postmenopausal endometrial cancer risk in the Norwegian Women and Cancer Study: a population-based prospective study. Bmc Womens Health. 2014;14.

135.   Weiderpass E, Sandin S, Lof M, Oh JK, Inoue M, Shimazu T, et al. Endometrial Cancer in Relation to Coffee, Tea, and Caffeine Consumption: A Prospective Cohort Study Among Middle-Aged Women in Sweden. Nutrition and Cancer-an International Journal. 2014;66(7):1132-43.

136.   Uccella S, Mariani A, Wang AH, Vierkant RA, Cliby WA, Robien K, et al. Intake of coffee, caffeine and other methylxanthines and risk of Type I vs Type II endometrial cancer. Brit J Cancer. 2013;109(7):1908-13.

137.   Hashibe M, Galeone C, Buys SS, Gren L, Boffetta P, Zhang ZF, et al. Coffee, tea, caffeine intake, and the risk of cancer in the PLCO cohort. Brit J Cancer. 2015;113(5):809-16.

138.   Shimazu T, Inoue M, Sasazuki S, Iwasaki M, Kurahashi N, Yamaji T, et al. Coffee consumption and risk of endometrial cancer: A prospective study in Japan. International Journal of Cancer. 2008;123(10):2406-10.

139.   Nilsson LM, Johansson I, Lenner P, Lindahl B, Van Guelpen B. Consumption of filtered and boiled coffee and the risk of incident cancer: a prospective cohort study. Cancer Cause Control. 2010;21(10):1533-44.

140.   Gunter MJ, Schaub JA, Xue XN, Freedman ND, Gaudet MM, Rohan TE, et al. A prospective investigation of coffee drinking and endometrial cancer incidence. International Journal of Cancer. 2012;131(4):E530-E6.

141.   Friberg E, Orsini N, Mantzoros CS, Wolk A. Coffee drinking and risk of endometrial cancer-A population-based cohort study. International Journal of Cancer. 2009;125(10):2413-7.

142.   Giri A, Sturgeon SR, Luisi N, Bertone-Johnson E, Balasubramanian R, Reeves KW. Caffeinated Coffee, Decaffeinated Coffee and Endometrial Cancer Risk: A Prospective Cohort Study among US Postmenopausal Women. Nutrients. 2011;3(11):937-50.

143.   Bandera EV, Williams-King MG, Sima C, Bayuga-Miller S, Pulick K, Wilcox H, et al. Coffee and tea consumption and endometrial cancer risk in a population-based study in New Jersey. Cancer Cause Control. 2010;21(9):1467-73.

144.   McCann SE, Yeh M, Rodabaugh K, Moysich KB. Higher regular coffee and tea consumption is associated with reduced endometrial cancer risk. International Journal of Cancer. 2009;124(7):1650-3.

145.   Terry P, Vainio H, Wolk A, Weiderpass E. Dietary factors in relation to endometrial cancer: A nationwide case-control study in Sweden. Nutrition and Cancer-an International Journal. 2002;42(1):25-32.
146.   Jain MG, Howe GR, Rohan TE. Nutritional factors and endometrial cancer in Ontario, Canada. Cancer Control. 2000;7(3):288-96.
147.   Kalandidi A, Tzonou A, Lipworth L, Gamatsi I, Filippa D, Trichopoulos D. A case-control study of endometrial cancer in relation to reproductive, somatometric, and life-style variables. Oncology. 1996;53(5):354-9.
148.   Petridou E, Koukoulomatis P, Dessypris N, Karalis D, Michalas S, Trichopoulos D. Why is endometrial cancer less common in Greece than in other European Union countries? Eur J Cancer Prev. 2002;11(5):427-32.
149.   Koizumi T, Nakaya N, Okamura C, Sato Y, Shimazu T, Nagase S, et al. Case-control study of coffee consumption and the risk of endometrial endometrioid adenocarcinoma. Eur J Cancer Prev. 2008;17(4):358-63.
150.   Hirose K, Niwa Y, Wakai K, Matsuo K, Nakanishi T, Tajima K. Coffee consumption and the risk of endometrial cancer: Evidence from a case-control study of female hormone-related cancers in Japan. Cancer Sci. 2007;98(3):411-5.
151.   Bhopal RS. Concepts of Epidemiology. 2nd ed. Oxford, UK: Oxford University press. 2008. p.90-2.
152.   Lund E, Kumle M, Braaten T, Hjartaker A, Bakken K, Eggen E, et al. External validity in a population-based national prospective study--the Norwegian Women and Cancer Study (NOWAC). Cancer Causes Control. 2003;14(10):1001-8.
153.   Weinehall L, Hallgren CG, Westman G, Janlert U, Wall S. Reduction of selection bias in primary prevention of cardiovascular disease through involvement of primary health care. Scand J Prim Health. 1998;16(3):171-6.
154.   Eriksson M, Stegmayr B, Lundberg V. MONICA quality assessments. Scand J Public Healt. 2003;31:25-30.
155.   Peltonen M, Huhtasaari F, Stegmayr B, Lundberg V, Asplund K. Secular trends in social patterning of cardiovascular risk factor levels in Sweden. The Northern Sweden MONICA Study 1986-1994. Multinational Monitoring of Trends and Determinants in Cardiovascular Disease. J Intern Med. 1998;244(1):1-9.
156.   Eriksson M, Holmgren L, Janlert U, Jansson JH, Lundblad D, Stegmayr B, et al. Large improvements in major cardiovascular risk factors in the population of northern Sweden: the MONICA study 1986-2009. J Intern Med. 2011;269(2):219-31.
157.   World Health Organization. Tobacco Free Initiative – Poverty [Internet]. [cited 24 May 2018]. Available from: http://www.who.int/tobacco/research/economics/rationale/poverty/en/
158.   Grimes DA, Schulz KF. Bias and causal associations in observational research. Lancet. 2002;359(9302):248-52.
159.   Hjartaker A, Andersen LF, Lund E. Comparison of diet measures from a food-frequency questionnaire with measures from repeated 24-hour dietary recalls. The Norwegian Women and Cancer Study. Public Health Nutr. 2007;10(10):1094-103.
160.   Borch KB, Ekelund U, Brage S, Lund E. Criterion validity of a 10-category scale for ranking physical activity in Norwegian women. Int J Behav Nutr Phys Act. 2012;9:2.
161.   Sheikh MA, Lund E, Braaten T. Test-retest reliability of self-reported diabetes diagnosis in the Norwegian Women and Cancer Study: A population-based longitudinal study (n =33,919). SAGE Open Med. 2016;4:2050312115622857.
162.   Skeie G, Mode N, Henningsen M, Borch KB. Validity of self-reported body mass index among middle-aged participants in the Norwegian Women and Cancer study. Clin Epidemiol. 2015;7:313-23.
163.   Johansson I, Hallmans G, Wikman A, Biessy C, Riboli E, Kaaks R. Validation and calibration of food-frequency questionnaire measurements in the Northern Sweden Health and Disease cohort. Public Health Nutr. 2002;5(3):487-96.
164.   Connor Gorber S, Schofield-Hurwitz S, Hardt J, Levasseur G, Tremblay M. The accuracy of self-reported smoking: a systematic review of the relationship between self-reported and cotinine-assessed smoking status. Nicotine Tob Res. 2009;11(1):12-24.

165.   Mansournia MA, Etminan M, Danaei G, Kaufman JS, Collins G. Handling time varying confounding in observational research. BMJ. 2017;359:j4587.

166.   Larsen IK, Smastuen M, Johannesen TB, Langmark F, Parkin DM, Bray F, et al. Data quality at the Cancer Registry of Norway: an overview of comparability, completeness, validity and timeliness. Eur J Cancer. 2009;45(7):1218-31.

167.   Barlow L, Westergren K, Holmberg L, Talback M. The completeness of the Swedish Cancer Register - a sample survey for year 1998. Acta Oncol. 2009;48(1):27-33.

168.   Pukkala E, Andersen A, Berglund G, Gislefoss R, Gudnason V, Hallmans G, et al. Nordic biological specimen banks as basis for studies of cancer causes and control - more than 2 million sample donors, 25 million person years and 100 000 prospective cancers. Acta Oncol. 2007;46(3):286-307.

169.   Fewell Z, Davey Smith G, Sterne JA. The impact of residual and unmeasured confounding in epidemiologic studies: a simulation study. Am J Epidemiol. 2007;166(6):646-55.

170.   Lee PH, Burstyn I. Identification of confounder in epidemiologic data contaminated by measurement error in covariates. BMC Med Res Methodol. 2016;16:54.

171.   Lee PH. Is a cutoff of 10% appropriate for the change-in-estimate criterion of confounder identification? J Epidemiol. 2014;24(2):161-7.

172.   Brown CR, Jacob P, 3rd, Wilson M, Benowitz NL. Changes in rate and pattern of caffeine metabolism after cigarette abstinence. Clin Pharmacol Ther. 1988;43(5):488-91.

173.   Parsons WD, Neims AH. Effect of smoking on caffeine clearance. Clin Pharmacol Ther. 1978;24(1):40-5.

174.   Bjorngaard JH, Nordestgaard AT, Taylor AE, Treur JL, Gabrielsen ME, Munafo MR, et al. Heavier smoking increases coffee consumption: findings from a Mendelian randomization analysis. International Journal of Epidemiology. 2017;46(6):1958-67.

175.   Groenwold RHH, Klungel OH, van der Graaf Y, Hoes AW, Moons KGM, Pharmacoepidemiologica PW. Adjustment for continuous confounders: an example of how to prevent residual confounding. Can Med Assoc J. 2013;185(5):401-6.

176.   Benowitz NL, Peng M, Jacob P, 3rd. Effects of cigarette smoking and carbon monoxide on chlorzoxazone and caffeine metabolism. Clin Pharmacol Ther. 2003;74(5):468-74.

177.   Bakuradze T, Boehm N, Janzowski C, Lang R, Hofmann T, Stockis JP, et al. Antioxidant-rich coffee reduces DNA damage, elevates glutathione status and contributes to weight control: results from an intervention study. Mol Nutr Food Res. 2011;55(5):793-7.

178.   Collomp K, Anselme F, Audran M, Gay JP, Chanal JL, Prefaut C. Effects of moderate exercise on the pharmacokinetics of caffeine. Eur J Clin Pharmacol. 1991;40(3):279-82.

179.   Zhang Z. Missing data imputation: focusing on single imputation. Ann Transl Med. 2016;4(1):9.

180.   Kenward MG, Carpenter J. Multiple imputation: current perspectives. Stat Methods Med Res. 2007;16(3):199-218.

181.   Steyerberg EW, van Veen M. Imputation is beneficial for handling missing data in predictive models. J Clin Epidemiol. 2007;60(9):979-.

182.   Galimard JE, Chevret S, Protopopescu C, Resche-Rigon M. A multiple imputation approach for MNAR mechanisms compatible with Heckman's model. Stat Med. 2016;35(17):2907-20.

183.   Azur MJ, Stuart EA, Frangakis C, Leaf PJ. Multiple imputation by chained equations: what is it and how does it work? Int J Meth Psych Res. 2011;20(1):40-9.

184.   White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. Stat Med. 2011;30(4):377-99.

185.   Lukic M, Licaj I, Lund E, Skeie G, Weiderpass E, Braaten T. Coffee consumption and the risk of cancer in the Norwegian Women and Cancer (NOWAC) Study. Eur J Epidemiol. 2016;31(9):905-16.

186.   Croxford R. Restricted Cubic Spline Regression: A Brief Introduction [Internet]. 2016. [cited 1 May 2018]. Available from: http://support.sas.com/resources/papers/proceedings16/5621-2016.pdf

187.	Royston P, Lambert PC. Flexible Parametric Survival Analysis Using Stata: Beyond the Cox Model. College Station, Texas: A Stata Press Publication. StataCorp LP, 2011. Chapter 1: Introduction: p.67-70.

188.	Stone CJ. Generalized Additive Models: Comment. Statist. Sci., Volume 1, Number 3 (1986), 312-314.

189.	Royston P, Parmar MKB. Flexible parametric proportional-hazards and proportional-odds models for censored survival data, with application to prognostic modelling and estimation of treatment effects. Stat Med. 2002;21(15):2175-97.

190.	Porta M. A Dictionary of Epidemiology, 5th Edition. Oxford University Press, 2014. DOI: 10.1093/acref/9780195314496.001.0001

191.	Lund E, Gram IT. Response rate according to title and length of questionnaire. Scand J Soc Med. 1998;26(2):154-60.

192.	Canchola AJ. Stewart SL. Bernstein L. West DW. Ross RK. Deapen DM. Pinder RM. Reynolds D. Wright W. Anton-Culver H. Peel D. Ziogas A. Horn-Ross PL. Cox Regression Using Different Time-scales [Intenet]. 2006. [cited 4 May 2018]. Available from: https://pdfs.semanticscholar.org/e0b2/8ba05620611e9ff477580c68cca98ef56d20.pdf?_ga=2.104704456.916259074.1529398745-503244253.1529398745

193.	Lamarca R, Alonso J, Gomez G, Munoz A. Left-truncated data with age as time scale: An alternative for survival analysis in the elderly population. J Gerontol a-Biol. 1998;53(5):M337-M43.

194.	Austin PC. Statistical power to detect violation of the proportional hazards assumption when using the Cox regression model. J Stat Comput Sim. 2018;88(3):533-52.

195.	Prince M. Epidemiology. In: Wright P. Stern J. Phelan M. (editors). Core Psychiatry. 3rd ed. Philadelphia, US: Saunders Elsevier. 2011. p.115-129.

196.	Borenstein M. Hedges LV. Higgins JPT. Rothstein HR. When Does it Make Sense to Perform a Meta-Analysis? In: Borenstein M. Hedges LV. Higgins JPT. Rothstein HR. Introduction to Meta-Analysis. Chichester UK: John Wiley & Sons, Ltd. 2009. doi: 10.1002/9780470743386.ch40 p. 357-60.

197.	Deeks JJ. Higgins JPT. Altman DG (editors). Analysing data and undertaking meta-analyses. In: Higgins JPT. Green S. (editors). Cochrane Handbook for Systematic Reviews of Interventions. Chichester UK: John Wiley & Sons, Ltd. 2008. p. 266-7. 276-84.

198.	von Hippel PT. The heterogeneity statistic I-2 can be biased in small meta-analyses. Bmc Med Res Methodol. 2015;15.

199.	Sterne JAC. Egger M. Moher D. (editors). Addressing reporting biases. In: Higgins JPT. Green S. (editors). Cochrane Handbook for Systematic Reviews of Interventions. Chichester UK: John Wiley & Sons, Ltd. 2008. p. 298-300.

200.	Hopewell S, Loudon K, Clarke MJ, Oxman AD, Dickersin K. Publication bias in clinical trials due to statistical significance or direction of trial results. Cochrane Db Syst Rev. 2009(1).

201.	Yu X, Bao Z, Zou J, Dong J. Coffee consumption and risk of cancers: a meta-analysis of cohort studies. BMC Cancer. 2011;11:96.

202.	Kurata R, Adachi M, Yamakawa O, Yoshimoto M. Growth suppression of human cancer cells by polyphenolics from sweetpotato (Ipomoea batatas L.) leaves. J Agric Food Chem. 2007;55(1):185-90.

203.	Matsunaga K, Katayama M, Sakata K, Kuno T, Yoshida K, Yamada Y, et al. Inhibitory Effects of Chlorogenic Acid on Azoxymethane-induced Colon Carcinogenesis in Male F344 Rats. Asian Pac J Cancer Prev. 2002;3(2):163-6.

204.	Xu R, Kang Q, Ren J, Li Z, Xu X. Antitumor Molecular Mechanism of Chlorogenic Acid on Inducting Genes GSK-3 beta and APC and Inhibiting Gene beta -Catenin. J Anal Methods Chem. 2013;2013:951319.

205.	Park GH, Song HM, Jeong JB. Kahweol from Coffee Induces Apoptosis by Upregulating Activating Transcription Factor 3 in Human Colorectal Cancer Cells. Biomol Ther (Seoul). 2017;25(3):337-43.

206.	Cavin C, Mace K, Offord EA, Schilter B. Protective effects of coffee diterpenes against aflatoxin B1-induced genotoxicity: mechanisms in rat and human cells. Food Chem Toxicol. 2001;39(6):549-56.

207.   Huber WW, Teitel CH, Coles BF, King RS, Wiese FW, Kaderlik KR, et al. Potential chemoprotective effects of the coffee components kahweol and cafestol palmitates via modification of hepatic N-acetyltransferase and glutathione S-transferase activities. Environ Mol Mutagen. 2004;44(4):265-76.

208.   Kotsopoulos J, Eliassen AH, Missmer SA, Hankinson SE, Tworoger SS. Relationship Between Caffeine Intake and Plasma Sex Hormone Concentrations in Premenopausal and Postmenopausal Women. Cancer. 2009;115(12):2765-74.

209.   Edling CE, Selvaggi F, Ghonaim R, Maffucci T, Falasca M. Caffeine and the analog CGS 15943 inhibit cancer cell growth by targeting the phosphoinositide 3-kinase/Akt pathway. Cancer Biol Ther. 2014;15(5):524-32.

210.   Jang MH, Shin MC, Kang IS, Baik HH, Cho YH, Chu JP, et al. Caffeine induces apoptosis in human neuroblastoma cell line SK-N-MC. J Korean Med Sci. 2002;17(5):674-8.

211.   Qi W, Qiao D, Martinez JD. Caffeine induces TP53-independent G(1)-phase arrest and apoptosis in human lung tumor cells in a dose-dependent manner. Radiat Res. 2002;157(2):166-74.

212.   He ZW, Ma WY, Hashimoto T, Bode AM, Yang CS, Dong ZG. Induction of apoptosis by caffeine is mediated by the p53, Bax, and caspase 3 pathways. Cancer Res. 2003;63(15):4396-401.

213.   Lafranconi A, Micek A, De Paoli P, Bimonte S, Rossi P, Quagliariello V, et al. Coffee Intake Decreases Risk of Postmenopausal Breast Cancer: A Dose-Response Meta-Analysis on Prospective Cohort Studies. Nutrients. 2018;10(2).

214.   Yaghjyan L, Rich S, Mao L, Mai V, Egan KM. Interactions of coffee consumption and postmenopausal hormone use in relation to breast cancer risk in UK Biobank. Cancer Causes Control. 2018.

215.   Bhoo Pathy N, Peeters P, van Gils C, Beulens JW, van der Graaf Y, Bueno-de-Mesquita B, et al. Coffee and tea intake and risk of breast cancer. Breast Cancer Res Treat. 2010;121(2):461-7.

216.   Ganmaa D, Willett WC, Li TY, Feskanich D, van Dam RM, Lopez-Garcia E, et al. Coffee, tea, caffeine and risk of breast cancer: a 22-year follow-up. Int J Cancer. 2008;122(9):2071-6.

217.   Hirvonen T, Mennen LI, de Bree A, Castetbon K, Galan P, Bertrais S, et al. Consumption of antioxidant-rich beverages and risk for breast cancer in French women. Ann Epidemiol. 2006;16(7):503-8.

218.   Fagherazzi G, Touillaud MS, Boutron-Ruault MC, Clavel-Chapelon F, Romieu I. No association between coffee, tea or caffeine consumption and breast cancer risk in a prospective cohort study. Public Health Nutrition. 2011;14(7):1315-20.

219.   Boggs DA, Palmer JR, Stampfer MJ, Spiegelman D, Adams-Campbell LL, Rosenberg L. Tea and coffee intake in relation to risk of breast cancer in the Black Women's Health Study. Cancer Causes Control. 2010;21(11):1941-8.

220.   Larsson SC, Bergkvist L, Wolk A. Coffee and black tea consumption and risk of breast cancer by estrogen and progesterone receptor status in a Swedish cohort. Cancer Causes Control. 2009;20(10):2039-44.

221.   Gierach GL, Freedman ND, Andaya A, Hollenbeck AR, Park Y, Schatzkin A, et al. Coffee intake and breast cancer risk in the NIH-AARP diet and health study cohort. Int J Cancer. 2012;131(2):452-60.

222.   Bhoo-Pathy N, Peeters PH, Uiterwaal CS, Bueno-de-Mesquita HB, Bulgiba AM, Bech BH, et al. Coffee and tea consumption and risk of pre- and postmenopausal breast cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort study. Breast Cancer Res. 2015;17:15.

223.   Oh JK, Sandin S, Strom P, Lof M, Adami HO, Weiderpass E. Prospective study of breast cancer in relation to coffee, tea and caffeine in Sweden. Int J Cancer. 2015;137(8):1979-89.

224.   Akter S, Kashino I, Mizoue T, Matsuo K, Ito H, Wakai K, et al. Coffee drinking and colorectal cancer risk: an evaluation based on a systematic review and meta-analysis among the Japanese population. Jpn J Clin Oncol. 2016;46(8):781-7.

225.   Dik VK, Bueno-de-Mesquita HB, Van Oijen MG, Siersema PD, Uiterwaal CS, Van Gils CH, et al. Coffee and tea consumption, genotype-based CYP1A2 and NAT2 activity and colorectal cancer risk-results from the EPIC cohort study. Int J Cancer. 2014;135(2):401-12.

226.   Dominianni C, Huang WY, Berndt S, Hayes RB, Ahn J. Prospective study of the relationship between coffee and tea with colorectal cancer risk: The PLCO Cancer Screening Trial. Brit J Cancer. 2013;109(5):1352-9.

227.   Peterson S, Yuan JM, Koh WP, Sun CL, Wang RW, Turesky RJ, et al. Coffee Intake and Risk of Colorectal Cancer Among Chinese in Singapore: The Singapore Chinese Health Study. Nutrition and Cancer-an International Journal. 2010;62(1):21-9.

228.   Naganuma T, Kuriyama S, Akhter M, Kakizaki M, Nakaya N, Matsuda-Ohmori K, et al. Coffee consumption and the risk of colorectal cancer: A prospective cohort study in Japan. International Journal of Cancer. 2007;120(7):1542-7.

229.   Groessl EJ, Allison MA, Larson JC, Ho SB, Snetslaar LG, Lane DS, et al. Coffee Consumption and the Incidence of Colorectal Cancer in Women. J Cancer Epidemiol. 2016;2016:6918431.

230.   Bidel S, Hu G, Jousilahti P, Antikainen R, Pukkala E, Hakulinen T, et al. Coffee consumption and risk of colorectal cancer. European Journal of Clinical Nutrition. 2010;64(9):917-23.

231.   Larsson SC, Bergkvist L, Giovannucci E, Wolk A. Coffee consumption and incidence of colorectal cancer in two prospective cohort studies of Swedish women and men. Am J Epidemiol. 2006;163(7):638-44.

232.   Michels KB, Willett WC, Fuchs CS, Giovannucci E. Coffee, tea, and caffeine consumption and incidence of colon and rectal cancer. J Natl Cancer I. 2005;97(4):282-92.

233.   Kashino I, Akter S, Mizoue T, Sawada N, Kotemori A, Matsuo K, et al. Coffee drinking and colorectal cancer and its subsites: A pooled analysis of 8 cohort studies in Japan. Int J Cancer. 2018.

234.   Sinha R, Cross AJ, Daniel CR, Graubard BI, Wu JW, Hollenbeck AR, et al. Caffeinated and decaffeinated coffee and tea intakes and risk of colorectal cancer in a large prospective study. American Journal of Clinical Nutrition. 2012;96(2):374-81.

235.   Steevens J, Schouten LJ, Verhage BAJ, Goldbohm RA, van den Brandt PA. Tea and coffee drinking and ovarian cancer risk: results from the Netherlands Cohort Study and a meta-analysis. Brit J Cancer. 2007;97(9):1291-4.

236.   Larsson SC, Wolk A. Coffee consumption is not associated with ovarian cancer incidence. Cancer Epidem Biomar. 2005;14(9):2273-4.

237.   Ong JS, Hwang LD, Cuellar-Partida G, Martin NG, Chenevix-Trench G, Quinn MCJ, et al. Assessment of moderate coffee consumption and risk of epithelial ovarian cancer: a Mendelian randomization study. Int J Epidemiol. 2017.

238.   Silvera SAN, Jain M, Howe GR, Miller AB, Rohan TE. Intake of coffee and tea and risk of ovarian cancer: A prospective cohort study. Nutrition and Cancer-an International Journal. 2007;58(1):22-7.

239.   Wang Y, Yu X, Wu Y, Zhang D. Coffee and tea consumption and risk of lung cancer: a dose-response analysis of observational studies. Lung Cancer. 2012;78(2):169-70.

240.   Guertin KA, Freedman ND, Loftfield E, Graubard BI, Caporaso NE, Sinha R. Coffee consumption and incidence of lung cancer in the NIH-AARP Diet and Health Study. Int J Epidemiol. 2016;45(3):929-39.

241.   Narita S, Saito E, Sawada N, Shimazu T, Yamaji T, Iwasaki M, et al. Coffee Consumption and Lung Cancer Risk: The Japan Public Health Center-Based Prospective Study. J Epidemiol. 2018;28(4):207-13.

242.   Hukkanen J, Jacob P, Peng M, Dempsey D, Benowitz NL. Effect of nicotine on cytochrome P450 1A2 activity. Brit J Clin Pharmaco. 2011;72(5):836-8.

243.   Sulem P, Gudbjartsson DF, Geller F, Prokopenko I, Feenstra B, Aben KK, et al. Sequence variants at CYP1A1-CYP1A2 and AHR associate with coffee consumption. Hum Mol Genet. 2011;20(10):2071-7.

244.   Yang A, Palmer AA, de Wit H. Genetics of caffeine consumption and responses to caffeine. Psychopharmacology (Berl). 2010;211(3):245-57.

245.   Deplanque G, Ceraline J, Mah-Becherel MC, Cazenave JP, Bergerat JP, Klein-Soyer C. Caffeine and the G2/M block override: a concept resulting from a misleading cell kinetic delay, independent of functional p53. Int J Cancer. 2001;94(3):363-9.

246.   Deplanque G, Vincent F, Mah-Becherel MC, Cazenave JP, Bergerat JP, Klein-Soyer C. Caffeine does not cause override of the G2/M block induced by UVc or gamma radiation in normal human skin fibroblasts. Br J Cancer. 2000;83(3):346-53.

247.   Muller WU, Bauch T, Wojcik A, Bocker W, Streffer C. Comet assay studies indicate that caffeine-mediated increase in radiation risk of embryos is due to inhibition of DNA repair. Mutagenesis. 1996;11(1):57-60.

248.   Stadler RH, Blank I, Varga N, Robert F, Hau J, Guy PA, et al. Acrylamide from Maillard reaction products. Nature. 2002;419(6906):449-50.

249.   Urban M, Kavvadias D, Riedel K, Scherer G, Tricker AR. Urinary mercapturic acids and a hemoglobin adduct for the dosimetry of acrylamide exposure in smokers and nonsmokers. Inhal Toxicol. 2006;18(10):831-9.

250.   Guenther H, Anklam E, Wenzl T, Stadler RH. Acrylamide in coffee: review of progress in analysis, formation and level reduction. Food Addit Contam. 2007;24 Suppl 1:60-70.

251.   Andrzejewski D, Roach JAG, Gay ML, Musser SM. Analysis of coffee for the presence of acrylamide by LC-MS/MS. J Agr Food Chem. 2004;52(7):1996-2002.

252.   Svensson K, Abramsson L, Becker W, Glynn A, Hellenas KE, Lind Y, et al. Dietary intake of acrylamide in Sweden. Food Chem Toxicol. 2003;41(11):1581-6.

253.   Mojska H, Gielecinska I. Studies of acrylamide level in coffee and coffee substitutes: influence of raw material and manufacturing conditions. Rocz Panstw Zakl Hig. 2013;64(3):173-81.

254.   Besaratinia A, Pfeifer GP. A review of mechanisms of acrylamide carcinogenicity. Carcinogenesis. 2007;28(3):519-28.

255.   Virk-Baker MK, Nagy TR, Barnes S, Groopman J. Dietary Acrylamide and Human Cancer: A Systematic Review of Literature. Nutrition and Cancer-an International Journal. 2014;66(5):774-90.

256.   Lipworth L, Sonderman JS, Tarone RE, McLaughlin JK. Review of epidemiologic studies of dietary acrylamide intake and the risk of cancer. Eur J Cancer Prev. 2012;21(4):375-86.

257.   Wijarnpreecha K, Thongprayoon C, Thamcharoen N, Panjawatanan P, Cheungpasitporn W. Association between coffee consumption and risk of renal cell carcinoma: a meta-analysis. Intern Med J. 2017;47(12):1422-32.

258.   Lee JE, Giovannucci E, Smith-Warner SA, Spiegelman D, Willett WC, Curhan GC. Total fluid intake and use of individual beverages and risk of renal cell cancer in two large cohorts. Cancer Epidem Biomar. 2006;15(6):1204-11.

259.   Allen NE, Balkwill A, Beral V, Green J, Reeves G, Million Women Study C. Fluid intake and incidence of renal cell carcinoma in UK women. Br J Cancer. 2011;104(9):1487-92.

260.   Zheng JS, Yang J, Fu YQ, Huang T, Huang YJ, Li D. Effects of Green Tea, Black Tea, and Coffee Consumption on the Risk of Esophageal Cancer: A Systematic Review and Meta-Analysis of Observational Studies. Nutrition and Cancer-an International Journal. 2013;65(1):1-16.

261.   Naganuma T, Kuriyama S, Kakizaki M, Sone T, Nakaya N, Ohmori-Matsuda K, et al. Coffee Consumption and the Risk of Oral, Pharyngeal, and Esophageal Cancers in Japan The Miyagi Cohort Study. Am J Epidemiol. 2008;168(12):1425-32.

262.   Zamora-Ros R, Lujan-Barroso L, Bueno-de-Mesquita HB, Dik VK, Boeing H, Steffen A, et al. Tea and coffee consumption and risk of esophageal cancer: The European prospective investigation into cancer and nutrition study. International Journal of Cancer. 2014;135(6):1470-9.

263.   Zhou YP, Tian CW, Jia CQ. A dose-response meta-analysis of coffee consumption and bladder cancer. Prev Med. 2012;55(1):14-22.

264.   Zeegers MP, Dorant E, Goldbohm RA, van den Brandt PA. Are coffee, tea, and total fluid consumption associated with bladder cancer risk? Results from the Netherlands Cohort Study. Cancer Causes Control. 2001;12(3):231-8.

265.   Sugiyama K, Sugawara Y, Tomata Y, Nishino Y, Fukao A, Tsuji I. The association between coffee consumption and bladder cancer incidence in a pooled analysis of the Miyagi Cohort Study and Ohsaki Cohort Study. Eur J Cancer Prev. 2017;26(2):125-30.

266.   Loftfield E, Freedman ND, Inoue-Choi M, Graubard BI, Sinha R. A Prospective Investigation of Coffee Drinking and Bladder Cancer Incidence in the United States. Epidemiology. 2017;28(5):685-93.

267.	Clavel J, Mandereau L, Limasset JC, Hemon D, Cordier S. Occupational exposure to polycyclic aromatic hydrocarbons and the risk of bladder cancer: a French case-control study. Int J Epidemiol. 1994;23(6):1145-53.
268.	Bonassi S, Merlo F, Pearce N, Puntoni R. Bladder cancer and occupational exposure to polycyclic aromatic hydrocarbons. Int J Cancer. 1989;44(4):648-51.
269.	Boada LD, Henriquez-Hernandez LA, Navarro P, Zumbado M, Almeida-Gonzalez M, Camacho M, et al. Exposure to polycyclic aromatic hydrocarbons (PAHs) and bladder cancer: evaluation from a gene-environment perspective in a hospital-based case-control study in the Canary Islands (Spain). Int J Occup Environ Health. 2015;21(1):23-30.
270.	Bosetti C, Boffetta P, La Vecchia C. Occupational exposures to polycyclic aromatic hydrocarbons, and respiratory and urinary tract cancers: a quantitative review to 2005. Ann Oncol. 2007;18(3):431-46.
271.	Nie K, Xing Z, Huang W, Wang W, Liu W. Coffee intake and risk of pancreatic cancer: an updated meta-analysis of prospective studies. Minerva Med. 2016;107(4):270-8.
272.	Guertin KA, Freedman ND, Loftfield E, Stolzenberg-Solomon RZ, Graubard BI, Sinha R. A prospective study of coffee intake and pancreatic cancer: results from the NIH-AARP Diet and Health Study. Br J Cancer. 2015;113(7):1081-5.
273.	Bidel S, Hu G, Jousilahti P, Pukkala E, Hakulinen T, Tuomilehto J. Coffee consumption and risk of gastric and pancreatic cancer - A prospective cohort study. International Journal of Cancer. 2013;132(7):1651-9.
274.	Michaud DS, Giovannucci E, Willett WC, Colditz GA, Fuchs CS. Coffee and alcohol consumption and the risk of pancreatic cancer in two prospective United States cohorts. Cancer Epidem Biomar. 2001;10(5):429-37.
275.	Bhoo-Pathy N, Uiterwaal CSPM, Dik VK, Jeurnink SM, Bech BH, Overvad K, et al. Intake of Coffee, Decaffeinated Coffee, or Tea Does Not Affect Risk for Pancreatic Cancer: Results From the European Prospective Investigation into Nutrition and Cancer Study. Clin Gastroenterol H. 2013;11(11):1486-92.
276.	Genkinger JM, Li RF, Spiegelman D, Anderson KE, Albanes D, Bergkvist L, et al. Coffee, Tea, and Sugar-Sweetened Carbonated Soft Drink Intake and Pancreatic Cancer Risk: A Pooled Analysis of 14 Cohort Studies. Cancer Epidem Biomar. 2012;21(2):305-18.
277.	Nilsson ML. Chapter 29 – Boiled Coffee: An Arctic Example of Potential Residual and Unmeasured Confounding in Coffee Epidemiology. In: Preedy V, editor. Coffee in Health and Disease Prevention. Massachusetts: Academic Press; 2014. p. 265-74.
278.	Jiang X, Zhang D, Jiang W. Coffee and caffeine intake and incidence of type 2 diabetes mellitus: a meta-analysis of prospective studies. Eur J Nutr. 2014;53(1):25-38.
279.	Carlstrom M, Larsson SC. Coffee consumption and reduced risk of developing type 2 diabetes: a systematic review with meta-analysis. Nutr Rev. 2018.
280.	Bosetti C, Rosato V, Li D, Silverman D, Petersen GM, Bracci PM, et al. Diabetes, antidiabetic medications, and pancreatic cancer risk: an analysis from the International Pancreatic Cancer Case-Control Consortium. Ann Oncol. 2014;25(10):2065-72.
281.	Gururajanna B, Al-Katib AA, Li YW, Aranha O, Vaitkevicius VK, Sarkar FH. Molecular effects of taxol and caffeine on pancreatic cancer cells. Int J Mol Med. 1999;4(5):501-7.
282.	Shen Z, Liu H, Cao H. Coffee consumption and risk of gastric cancer: an updated meta-analysis. Clin Res Hepatol Gastroenterol. 2015;39(2):245-53.
283.	Xie F, Wang D, Huang Z, Guo Y. Coffee consumption and risk of gastric cancer: a large updated meta-analysis of prospective studies. Nutrients. 2014;6(9):3734-46.
284.	Sanikini H, Dik VK, Siersema PD, Bhoo-Pathy N, Uiterwaal CS, Peeters PH, et al. Total, caffeinated and decaffeinated coffee and tea intake and gastric cancer risk: results from the EPIC cohort study. Int J Cancer. 2015;136(6):E720-30.
285.	Larsson SC, Giovannucci E, Wolk A. Coffee consumption and stomach cancer risk in a cohort of Swedish women. Int J Cancer. 2006;119(9):2186-9.
286.	Ainslie-Waldman CE, Koh WP, Jin AZ, Yeoh KG, Zhu F, Wang RW, et al. Coffee Intake and Gastric Cancer Risk: The Singapore Chinese Health Study. Cancer Epidem Biomar. 2014;23(4):638-47.

287.   Bravi F, Scotti L, Bosetti C, Gallus S, Negri E, La Vecchia C, et al. Coffee drinking and endometrial cancer risk: a metaanalysis of observational studies. Am J Obstet Gynecol. 2009;200(2):130-5.

288.   Je Y, Giovannucci E. Coffee consumption and risk of endometrial cancer: Findings from a large up-to-date meta-analysis. International Journal of Cancer. 2012;131(7):1700-10.

289.   Wang AQ, Wang SS, Zhu CP, Huang HC, Wu LC, Wan XS, et al. Coffee and cancer risk: A meta-analysis of prospective observational studies. Sci Rep-Uk. 2016;6.

290.   Friberg E, Mantzoros CS, Wolk A. Diabetes and risk of endometrial cancer: a population-based prospective cohort study. Cancer Epidemiol Biomarkers Prev. 2007;16(2):276-80.

291.   Saltzman BS, Doherty JA, Hill DA, Beresford SA, Voigt LF, Chen C, et al. Diabetes and endometrial cancer: an evaluation of the modifying effects of other known risk factors. Am J Epidemiol. 2008;167(5):607-14.

292.   Lucenteforte E, Bosetti C, Talamini R, Montella M, Zucchetto A, Pelucchi C, et al. Diabetes and endometrial cancer: effect modification by body weight, physical activity and hypertension. Br J Cancer. 2007;97(7):995-8.

293.   Cardenas C, Quesada AR, Medina MA. Insights on the antitumor effects of kahweol on human breast cancer: Decreased survival and increased production of reactive oxygen species and cytotoxicity. Biochem Bioph Res Co. 2014;447(3):452-8.

294.   Wu T, Willett WC, Hankinson SE, Giovannucci E. Caffeinated coffee, decaffeinated coffee, and caffeine in relation to plasma C-peptide levels, a marker of insulin secretion, in U.S. women. Diabetes Care. 2005;28(6):1390-6.

295.   Cust AE, Allen NE, Rinaldi S, Dossus L, Friedenreich C, Olsen A, et al. Serum levels of C-peptide, IGFBP-1 and IGFBP-2 and endometrial cancer risk; results from the European prospective investigation into cancer and nutrition. Int J Cancer. 2007;120(12):2656-64.

296.   Lukanova A, Zeleniuch-Jacquotte A, Lundin E, Michel A, Arslan AA, Rinaldi S, et al. Prediagnostic levels of C-peptide, IGF-I, IGFBP-1,-2 and-3. International Journal of Cancer. 2004;108(2):262-8.

297.   Williams CJ, Fargnoli JL, Hwang JJ, van Dam RM, Blackburn GL, Hu FB, et al. Coffee consumption is associated with higher plasma adiponectin concentrations in women with or without type 2 diabetes - A prospective cohort study. Diabetes Care. 2008;31(3):504-7.

298.   Yamashita K, Yatsuya H, Muramatsu T, Toyoshima H, Murohara T, Tamakoshi K. Association of coffee consumption with serum adiponectin, leptin, inflammation and metabolic markers in Japanese workers: a cross-sectional study. Nutr Diabetes. 2012;2.

299.   Dalamaga M, Diakopoulos KN, Mantzoros CS. The Role of Adiponectin in Cancer: A Review of Current Evidence. Endocr Rev. 2012;33(4):547-94.

300.   Li ZJ, Yang XL, Yao Y, Han WQ, Li B. Circulating adiponectin levels and risk of endometrial cancer: Systematic review and meta-analysis. Exp Ther Med. 2016;11(6):2305-13.

301.   Allen NE, Key TJ, Dossus L, Rinaldi S, Cust A, Lukanova A, et al. Endogenous sex hormones and endometrial cancer risk in women in the European Prospective Investigation into Cancer and Nutrition (EPIC). Endocr-Relat Cancer. 2008;15(2):485-97.

302.   Ferrini RL, BarrettConnor E. Caffeine intake and endogenous sex steroid levels in postmenopausal women - The Rancho Bernardo Study. Am J Epidemiol. 1996;144(7):642-4.

303.   Nagata C, Kabuto M, Shimizu H. Association of coffee, green tea, and caffeine intakes with serum concentrations of estradiol and sex hormone-binding globulin in premenopausal Japanese women. Nutrition and Cancer-an International Journal. 1998;30(1):21-4.

304.   London S, Willett W, Longcope C, Mckinlay S. Alcohol and Other Dietary Factors in Relation to Serum Hormone Concentrations in Women at Climacteric. American Journal of Clinical Nutrition. 1991;53(1):166-71.

Paper 1

Lukic M, Licaj I, Lund E, Skeie G, Weiderpass E, Braaten T.

Coffee consumption and the risk of cancer in the Norwegian Women and Cancer (NOWAC) Study.

Paper 2

Lukic M, Nilsson LM, Skeie G, Lindahl B, Braaten T.

Coffee consumption and risk of rare cancers in Scandinavian countries.

Paper 3

Lukic M, Guha N, Licaj I, van den Brandt PA, Stayner LT, Tavani A, et al.

Coffee Drinking and the Risk of Endometrial Cancer: An Updated Meta-Analysis of Observational Studies.

APPENDIX

Questionnaire

WOMEN AND CANCER Confidential Autumn 2004
If you agree to take part, tick YES in the box to the right.
If you do not wish to take part, avoid reminders by ticking NO and return
the questionnaire in the envelope provided.
We ask you to fill out the questionnaire as accurately as possible.

The questionnaire is to be read optically. Please use blue or black pen. Use of comma is not allowed,
round up from 0.5 to 1. Use block letters.

I agree to
take part in
YES
the questionnaire
survey NO

Best wishes,
Eiliv Lund
Professor dr. med.

Menopause
Do you still have regular periods?
… Yes
… Have irregular periods
… Unknown (Absent because of illness, etc.)
… Unknown (Current use of medication containing estrogen)
… No
> **If No;**
>> Have they stopped of their own accord? .....
>> Have both your fallopian tubes been removed?...
>> Have you had your womb removed (hysterectomy)?...
>> Other? …

Age when periods stopped? .....years

Pregnancies, births and breastfeeding
Have you ever been pregnant? Yes/No
> **If Yes; how many children have you born totally?** .....children
> **How old were you at last birth?** .....years

Use of contraceptive pill
Have you ever used the pill or minipill Yes/No
> **If Yes; In how many years have you used the pill totally?** .....years
> **Are you currently on the pill?** Yes/No

Use of hormone preparations with estrogen in menopause
Have you ever used estrogen pills/plasters? Yes/No
> **If Yes;** how long have you used estrogen pills/plasters in all? .....years
> **How old were you when you first used estrogen pills/plasters?** .....years
> **Are you currently using pills/plasters?** Yes/No

If you replied "Yes", we ask you to elaborate further on this by answering the questions below. For each period
of continuous use of the same estrogen preparation, we hope you can tell us how old you were when you started,
how long you used the same hormone preparation, and what it was called. If you stopped using it for a while, or
switched to other preparations, you should count this as a new period. If you cannot remember the name of the
hormone preparation, write 'Unsure'. To help you remember the names of estrogen preparations, please use the
brochure provided, which contains pictures of estrogen preparations that have been sold in Norway. Please also
give the number of the estrogen pill/plaster given in the brochure.

	Age at start	Used same estrogen pill/plaster continuously from 1998			Name of estrogen pill/plaster (see brouchure)
		Year	Month	Nr	
1.					
2.					
3.					
4.					
5.					

Estrogen preparations for vaginal use
Have you ever used estrogen creams/suppositories? Yes/No
        If Yes; Are you currently using creams/suppositories? Yes/No

Intrauterine device
Have you ever used an intrauterine device (Levonova)? Yes/No
        If Yes; for how long have you used an IUD all together? ….. years
        How old were you the first time you got an IUD inserted? ….. years
        Are you currently using an IUD? Yes/No

Self-perceived health
Do you rate your own current state of health as (tick one box only):
… Very good …Good …Poor … Very poor

Illness
Do you have or have you had any of the following illnesses? (tick one or more boxes)
                    Yes/ No - If Yes, age when first discovered

Cancer
High blood pressure
Heart failure/heart cramps
Heart attack
Stroke
Diabetes
Depression (seen a doctor)
Hypothyreosis

For the following conditions, tick which year they emerged, or give the year for the period before 1991.
                    before 98   98   99   00   01   02   03

Muscle pains (myalgia)
Fibromyalgia/fibrositis
Chronical fatigue syndrome
Backpains of unknown cause
Whiplash
Osteoporosis
Fractures
        Forearm (wrist)
        Spine (compression)
        Other fractures, describe.........

Other medication
Do you currently use any of these preparations daily? Yes/No
Fontex, Fluoxetin
Cipramil, Citalopram, Desital
Seroxat, Paroxetin
Zoloft
Fevarin
Cipralex
        If Yes; for how long time have you used this preparation continuously? Months….. Years…..
Have you ever used any of these preparations? Yes/No
        If Yes; For how long time did you use these preparations continuously? Months….. Years…..

Height and weight

How tall are you? …..cm
How much do you weigh at the moment? …..kg
What was your weight at age 18? …..kg
Body type 1.st degree (tick one box only):
….Very thin …. Thin ….Normal ….Heavy ….Very heavy

Smoking habits

During life, have you smoked more than 100 cigarettes totally? Yes/No
  If yes, please fill in how many cigarettes you smoked on average per day the last five years.
      Number of cigarettes smoked per day
  0   1-4   5-9   10-14   15-19   20-24   25+
How old were you when you smoked your first cigarette? ….. years
Do you smoke on a daily basis at the moment? Yes/No
  If No, how old were you when you quit? ….. years
Did any of your parents smoke when you were child? Yes/No
  If Yes, how many cigarettes did they smoke in total per day? …. cigarettes

Breast cancer in the family

Have any of your close relatives had breast cancer:

	Yes	No	Unknown	Age at start
Daughter				
Mother				
Sister				

Mammography screening

Have you ever been to mammography screening of your breasts? Yes/No
  If Yes; How old were you first time? ….. years
How many times have you been screened?
- After invitation from the Mammography Programme ….. times
- After referral from doctor ….. times
- Without referral from doctor ….. times

Physical activity

Please indicate the level of your physical activity on a scale from very low to very high by age 14, 30 and today. The scale goes from 1-10. By physical activity we mean both work in and outside the home, as well as training/exercise and other physical activity, such as walking, etc.

Age	Very low		Very high
14 years	1 2 3 4 5	6 7 8 9 10	
30 years	1 2 3 4 5	6 7 8 9 10	
Today	1 2 3 4 5	6 7 8 9 10	

How many hours per day do you walk or stroll ourdoors at mean?

	Seldom/ Never	Less than ½ hour	½-1 hour	1-2 hours	more than 2 hours
Winter					
Spring					
Summer					
Autumn					

How many stairs (whole floors) do you walk per day on average? ……….
For each of the following activities you partake in, we ask you to estimate <u>how many minutes per day</u> you use on these activities on average.

Minutes

Activity	Winter	Spring	Summer	Fall
Watch TV				
Reading				
Handicraft				

Gardening
Shower/bath/
personal care
Exercise/jogging
Bicycling

How many hours per day on the workplace do you on average use to   **Hours**
Sit……………………………………………………
Stand………………………………………………….
Walk………………………………………………….
Lift……………………………………………………
Heavy lifting/caretaking…………………………..

Diet
Do any of the following affect your diet? (More than one tick allowed)
Vegetarian… Do not eat Norwegian diet on daily basis… Have allergy/intolerance… Chronic illness…
Anorexia…
Bulimia… Try to lose weight… Low GI food…

We are interested in finding out about your <u>usual</u> eating habits. For each question, tick how often in the <u>last twelve months</u> you have eaten the food in question, and how much you usually eat/drink each time.

Drink
How many glasses of each kind of milk do you usually drink? (Tick one box on each line).

	Never/ seldom	1-4 wk	5-6 wk	1/ day	2-3/ day	4+/ day
Full cream milk (sweet, sour)						
Semi-skimmed milk (sweet, sour)						
Extra skimmed milk						
Skimmed milk (sweet, sour)						

How many cups of each kind of coffee/tea do you usually drink? (Tick one box on each line)

	Never/ seldom	1-6 wk	1/ day	2-3/ day	4-5/ day	6-7/ day	8+/ day
Boiled coffee (kokekaffe)							
Filter coffee							
Instant coffee							
Black tea							
Green tea							

Do you use the following in coffee or tea:

	Coffee	Tea
Sugar (non-artificial sweetener)	Yes/No	Yes/No
Milk or cream	Yes/No	Yes/No

How many glasses of water do you usually drink?

	Never/ seldom	1-6 wk	1/ day	2-3/ day	4-5/ day	6-7/ day	8+/ day
Tap water and bottled water							

How many glasses of juice, limonade and soft drinks do you usually drink? (Tick one box on each line)

	Never/ seldom	1-4 wk	5-6 wk	1/ day	2-3/ day	4+/ day
Orange juice						
Lemonade/soft drinks with sugar						
Lemonade/soft drinks with sugar						
Sugarfree lemonade/soft drinks						

Yoghurt/cereals
How often do you eat yoghurt (equivalent to 1 carton)? (Tick one box only)
.....never/seldom ....1/wk .....2-3/wk ....4+/wk

How often do you eat cereals, oat flakes or muesli? (Tick one box only)
.....never/seldom .....1-3/wk .....4-6/wk 1/day

Bread
How many slices of bread/rolls and crispbread do you normally eat? (1/2 roll = 1 slice of bread) (Tick one box on each line)

	Never/ seldom	1-4 wk	5-7/ wk	2-3/ day	4-5/ day	6+ day
Wholemeal bread						
Kneippbrød (semi white)						
White bread						
Crispbread, etc.						

Below are some questions on use of various kinds of sandwich filling/spread. We want to know how many slices of bread with these fillings/spreads you usually eat. If you also use these products on other things than bread (e.g., on waffles, in breakfast cereals, porridge), please take this into account when answering the questions.

How many slices of bread do you eat with? (Tick one box on each line)

	Never/ seldom	1-3 wk	4-6/ wk	1/ day	2-3/ day	4+/ day
Jam						
Brown cheese, full cream						
Brown cheese, low-fat						
White cheese, full cream						
White cheese, low-fat						
Meat fillings/spreads, liver paté						
Shrimp salad, Italian salad, etc.						

How many slices of bread per week on average in the last twelve months have you eaten with? (Tick one box on each line)

	Never/ seldom	1/ wk	2-3/ wk	4-6/ week	7-9/ week	10+/ week
Mackerel in tomato sauce, smoked mackerel						
Caviar						
Herring/Anchovies						
Salmon (cured and smoked)						
Other fish fillings/spreads						

What kind of fat do you usually spread on your bread? (Tick more than one box if necessary)
..... I do not use fat on bread
..... butter
..... hard margarine (e.g., Per, Melange)
..... soft margarine (e.g., Soft)
..... margarine/butter mix (e.g., Bremykt)
..... Brelett
..... low-fat margarine (e.g., Soft light, Letta)
…. Middle fat margarine (Olivero, Omega)

If you use fat on your bread, how thick a layer do you usually spread on it? (Tick one box only)
.... very thin scraping (3g)   ..... thin layer (5g)
..... well-covered (8g)   .... thick layer (12g)

Fruits and vegetables
How often do you eat fruit? (Tick one box per line only)

	Never/ seldom	1-3 month	1/ wk	2-4/ wk	5-6/ wk	1/ day	2+/ day
Apples/pears							
Oranges, etc.							
Bananas							
Other fruit							

How often do you eat various kinds of vegetables? (Tick one box per line)

	Never/ seldom	1-3 month	1/ wk	2/ wk	3/ wk	4-5/ wk	6-7/ wk
Carrots							
Cabbage							
Turnip							
Broccoli/cauliflower							
Mixed salad							
Tomatoes							
Mixed vegetables (frozen)							
Onions							
Other vegetables							

For the vegetables you eat, tick how much you eat each time. (Tick one box for each kind)
- carrots ....1/2 .....1 .....1 1/2 .....2+
- cabbage .....1/2dl .....1dl .....11/2dl .....2+dl
- turnip .....1/2dl .....1dl .....11/2dl .....2+dl
- broccoli/cauliflower .....1-2 rosette(s) .....3-4 rosettes .....5+ rosettes
- mixed salad .....1dl .....2dl .....3dl .....4+dl
- tomatoes ….1/4 ….1/2 ….1 ….2+
- mixed vegetables .....1/2dl .....1dl .....2dl .....3+dl

How many potatoes do you usually eat (boiled, fried, mashed)? (Tick one box)
..... I do not/I seldom eat potatoes
..... 1-4/wk .....5-6/wk ..... 1/day ..... 2/day ..... 3/day .....4+/day

Rice, spaghetti, porridge, soup
How often do you eat rice and spaghetti/macaroni? (Tick one box on each line)

	Never/ seldom	1/ month	1/ wk	2/ wk	3+/ wk
Rice					
Spaghetti, macaroni, noodles					

How often do you eat porridge? (Tick one box only)

	Never/ seldom	1/ month	2-3/ month	1/ wk	2-6/ wk	1+/ day
Rice porridge						
Other porridge (oatmeal, etc.)						

How often do you eat soup? (Tick one box on each line)

	Never/ seldom	1/ month	1/ wk	2/ wk	3+/ wk
As main course					
As appetizer/lunch/evening meal					

Fish
We would like to know how often you eat fish. Please fill in answers to the questions on fish consumption as fully as possible. The availability of fish may vary throughout the year. Please indicate in which seasons you eat the different kinds of fish.

	Never/ seldom	Same amount all year	Winter	Spring	Summer	Fall
Cod, saithe, halibut, pollack						
Wolffish, flounder, redfish						
Salmon, trout						
Mackerel						
Herring						
Other fish types						

In the periods of the year when you eat fish, how often do you usually eat the following? (Tick one box per line)

	Never/ seldom	1/ month	2-3/ month	1/ wk	2+/ wk

Boiled cod, saithe, halibut, pollack
Fried cod, saithe, halibut, pollack
Wolffish, flounder, redfish
Salmon, trout
Mackerel
Herring
Other fish types

If you eat fish, how much do you usually eat each time? (1slice/piece = 150g) (Tick one box on each line)
- boiled fish (slice).....1 .....1.5 .....2 .....3+
- fried fish (piece).....1 .....1.5 .....2 .....3+

How many times per year do you eat fish feed? (Tick one box only per line)

	0	1-3	4-6	7-9	10+
Roe					
Fish liver					

If you eat fish liver, how many tablespoonfuls do you usually take each time? (Tick one box only)
.....1 .....2 .....3-4 .....5-6 .....7+

How often do you eat the following kinds of fish dish? (Tick one box only per line)

	Never/ seldom	1/ month	2-3/ month	1/ wk	2+/ wk
Fishcakes/pudding/balls					
Fish stew, fish pie					
Fried fish (in batter), fish fingers					

How much do you usually eat of the various dishes? (Tick one box only on each line)
Fishcakes/pudding/balls (pcs.) (2 fish balls = 1 fishcake).....1 .....2 .....3 .....4+
Fish stew, fish pie (dl).....1-2 .....3-4 .....5+
Fried fish (in batter), fish fingers (pcs.) .....1-2 .....3-4 .....5-6 .....7+

In addition to information regarding fish consumption, it is important to gather information on the accompaniments served with fish. How often do you use the following together with fish? (Tick one box per line only)

	Never/ seldom	1/ month	2-3/ month	1/ wk	2+/ wk
Melted or solid butter					
Melted or solid margarine					
Clotted cream (35%)					
Reduced-fat cream (20%)					
Sauce containing fat (white/brown)					
Non-fat sauce (white/brown)					

For the various kinds of accompaniments you eat with fish, please tick how much you would normally eat.
Melted or solid butter (tbs) .....1/2 .....1 .....2-3 .....4+
Melted or solid margarine (tbs) .....1/2 .....1 .....2-3 .....4+
Clotted cream (tbs) .....1/2 .....1 .....2-3 .....4+
Reduced-fat cream (tbs)....1/2 .....1 .....2-3 .....4+
Sauce containing fat (dl)...1/4 ....1/2.....3/4 .....1 .....2+
Non-fat sauce (dl) ....1/4 .....1/2 ....3/4....1 .....2+

How often do you eat shellfish (e.g., shrimp, crab)? (Tick one box only)
..... never/seldom ..... 1/mth ..... 2-3/mth .....1+/wk

Meat
How often do you eat reindeer meat?
... Never/seldom …1/month …2-3/month… 1 /wk … 2-3/wk … 4+/wk

How often do you usually eat the following meat and poultry dishes? (Tick only one box for each dish)

	Never/ seldom	1/ month	2-3/ month	1/ wk	2+/ wk

Steak (cow, pork, mutton)
Chops
Beef
Meat balls, patties
Sausages
Stews, hash
Pizza with meat
Chicken
Bacon, pork
Other meat dishes

If you eat the following dishes, how much do you usually eat? (Tick one box per line)
Steak (slices) .....1 .....2 .....3 .....4 … 5+
- Chops (pcs.) .....1/2 .....1 .....1.5 .....2+
- meat balls, - cakes (pcs.) .....1 .....2 ......3 .....4+
- sausages (pcs.a 150g) ....1/2 .....1 .....1.5 .....2+
- stew, hash (dl) .....1-2 .....3 .....4 .....5+
- pizza with meat (pcs a 100g) ....1 .....2 .....3 .....4+

Which sauces do you use to meat dishes and pasta dishes?

	Never/ seldom	1/ month	2-3/ month	1/ wk	2-6/ wk	1+/ day
Gravy						
Broth						
Tomato sauce						
Creamy sauce						

How much do you usually eat of these sauces?
Gravy (dl) …1/4 …1/2 …3/4 …1 …2+
Broth …1/4 …1/2 …3/4 …1 …2+
Tomato sauce …1/4 …1/2 …3/4 …1 …2+
Creamy sauce …1/4 …1/2 …3/4 …1 …2+

Other types of food
How many eggs do you usually eat in the course of a week (fried, boiled, scrambled, omelette)? (Tick one box)
.....0 .....1 .....2 .....3-4 .....5-6 .....7+

How often do you eat ice cream (for dessert, ice lollies, etc.)?
(Tick once to indicate how often you eat ice cream in summer, and once for the rest of the year)

	Never/ seldom	1/ month	2-3/ month	1/ wk	2-6/ wk	1+/ day
- in summer						
- rest of the year						

How much ice cream do you normally eat each time? (Tick one box)
.....1dl .....2dl .....3dl .....4+dl

How often do you eat sweet buns, cakes, Danish pastry, waffles, etc. (Tick one box)

	Never/ seldom	1-3/ month	1/ wk	2-3/ wk	4-6/ wk	1+/ day
Yeast baking (buns, etc.)						
Pastry(Danish, cream-filled)						
Cakes						
Pancakes						
Waffles						
Biscuits, cookies						
Lefser/lomper (Norwegian specialities)						

How often do you eat dessert? (Tick one box)

	Never/ seldom	1-3/ month	1/ wk	2-3/ wk	4-6/ wk	1+/ day
Pudding (chocolate, caramel)						
Ricecream ,mousse						
Compote, fruit porridge, canned fruits						
Strawberries (fresh, frozen)						
Other berries (fresh, frozen)						

How often do you eat chocolate? (Tick one box)

	Never/ seldom	1-3/ month	1/ wk	2-3/ wk	4-6/ wk	1+/ day
Dark chocolate						
Light chocolate						

If you eat chocolate, how much do you usually eat each time?
Use the size of a Kvikk-Lunsj (Kit-Kat) as a guide, and indicate how much you eat in relation to that) (Tick one box)
.....1/4 .....1/2 .....3/4 .....1 .....1.5 .....2+

How often do you eat salty snacks? (Tick one box)

	Never/ seldom	1-3/ month	1/ wk	2-3/ wk	4-6/ wk	1+/ day
Potato chips						
Peanuts						
Other nuts						
Other snacks						

Cod liver oil and fish oil capsules
Do you use cod liver oil (liquid)? Yes/No
    If yes, how often do you use it? (Tick one box for each line)

	Never/ seldom	1-3/ month	1/ wk	2-6/ wk	Daily
- in the winter					
- the rest of the year					

How much cod liver oil do you usually take at one time?
.....1ts .....1/2ts .....1+ts

Do you use cod liver oil pills/capsules? Yes/No
    If yes, how often do you take cod liver oil pills/capsules? (Tick one box for each line)

	Never/ seldom	1-3/ month	1/ wk	2-6/ wk	Daily
- in the winter					
- the rest of the year					

Which type of cod liver oil pills/capsules do you usually use, and how many do you use to take each time?
Name……………Amount……

Dietary supplements
Do you use other dietary supplements? Yes/No
    If yes, how often do you take such supplements?

	Never/ seldom	1-3/ month	1/ wk	2-6/ wk	Daily
Brand name:..................................					
Brand name:..................................					
Brand name:..................................					

Warm meals
How many times during a moth do you eat warm meals?
… Breakfast   …Dinner
… Lunch   … Evening meal

Alcohol
Are you a teetotaller? Yes/No

> **If No, how often and how much have you drunk on average in the last twelve months?**
> (Tick one box on each line)

	Never/ seldom	1/ month	2-3/ month	1/ wk	2-4/ wk	5-6/ wk	1/ day	2+/ day
Beer (1/2l)								
Wine (glass)								
Spirits (shorts/cocktails)								
Liqeuers								

Social conditions
Are you (tick one box only):
.....married ....cohabitant ....single…other …divorced …widow

How many persons are there in your household? Number: .....

What is your household's gross annual income?
.....less than 150 000 kr .....151 000-300 000 kr
.....301 000-450 000 kr .....451 000-600 000 kr
.....more than 750 000 kr

What is your work situation?
… work full time … work part-time …retired … work at home …education …disabled … rehabilitation …unemployed

Do you work outdoors in your job? Yes/No
> **If Yes; how many hours per week?** …Summer …Winter

Sun habits
Do you get freckles when you sunbathe? Yes/No

To study the effect of sunbathing on risk of melanoma, we ask you to give information about skin colour.
Tick on the colour that best matches your skin colour (without sunbathing).
(coloured scale 1-10)

How many times per year have you been sunburnt to the extent that you skin has become irritated and blistered, and peeled afterwards? (One tick for each age-group)

Age	Never	Max 1/ year	2-3/ year	4-5/ year	6 or more/ year
40-49					
50+					

How many weeks on average per year have you taken sunbathes in southern Europe?

Age	Never	1 wk	2-3 wk	4-5 wk	7+wk
40-49					
50+					
The last 12 months					

How often have you been sunbathing in solarium?

Age	Never	Seldom	1/month	2-3/month	3-4/month	1+/wk
40-49						
50+						
The last 12 months						

How often do you shower or take a bath?

	1+/ day	1/ day	4-6/ wk	2-3/ wk	1/ wk	2-3/ month	Seldom/ never
With soap/shampoo							
Without soap/shampoo							

When do you use cream with sun screen? (more than one tick possible)
....At Easter ....in Norway or outside southern Europe? ....sunbathing in southern Europe

Which sun factors do/did you use in these periods?

	None	1-4	5-9	10-14	15+
Easter					
Norway/outside south Europe					
South Europe					

How many irregularly shaped moles larger than 5mm do you have in total on both legs (between the toes and the groin)? Three examples of moles larger than 5mm are shown below.
.....0 .....1 .....2-3 .....4-6 .....7-12 .....13-24 .....25+

How often do you use the following skin care products? (Tick one box)

	Never/ seldom	1/ month	2-3/ month	1/ wk	2-4/ wk	5-6/ wk	1/ day	2+/ day
Face cream								
Hand cream								
Body lotion								
Perfume								

Finally we would ask about your permission to contact you again per post. We will get your address from the central person registry. Yes/No
Are you willing to give a blood sample? Yes/No