DIET AND ENDOMETRIAL CANCER

Insulin related factors

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Till min familj
ABSTRACT

There is accumulating evidence that insulin resistance and hyperinsulinemia are involved in the etiology of endometrial cancer. Dietary intake can influence insulin levels especially among individuals who are already insulin resistant.

Coffee drinking has been reported to have beneficial effects on insulin sensitivity. Glycemic index and load are concepts developed to quantify the glycemic response and insulin demand to carbohydrates in different foods. A moderate alcohol intake has been shown to improve insulin sensitivity whereas a higher intake has been shown to increase estrogen levels which unbalanced by progesterone may increase the risk of endometrial cancer. In the analyses we used data from the Swedish Mammography Cohort, a population-based prospective cohort study including over 60,000 women, born 1914-48, among whom 689 endometrioid adenocarcinoma cases were diagnosed through 2007 (17.6 years of follow-up). We examined the association between coffee consumption, carbohydrate intake, glycemic index, glycemic load and alcohol consumption at baseline 1987-90 and in 1997 and endometrial cancer risk using Cox proportional hazards models.

To quantitatively summarize the association between alcohol, diabetes and the risk of endometrial cancer, we conducted meta-analyses of published studies. In the meta-analyses we identified studies by literature searches of the databases PubMed and Embase and by searching the reference lists of relevant articles. We summarized the relative risks (RRs) with 95% confidence intervals (CIs) using random-effects models and in the meta-analysis of alcohol also with a dose-response random-effect meta-regression model.

Drinking four cups or more of coffee per day was overall associated with a 25% decreased risk of endometrial cancer as compared to one cup of coffee or less per day. The association seemed to be largely confined to overweight and obese women.

We observed no overall association between carbohydrate intake, glycemic index, or glycemic load and the incidence of endometrial cancer. Among overweight and obese women with low physical activity, who completed the questionnaire in 1997, carbohydrate intake and glycemic load were positively related to endometrial cancer risk. In this subgroup, the RRs comparing extreme quartiles were 1.90 (95% CI 0.84-4.31) for carbohydrate intake and 2.99 (95% CI 1.17-7.67) for glycemic load.

We observed no association between alcohol and endometrial cancer risk in the Swedish elderly study population with a generally low consumption. However, in the meta-analysis of alcohol and endometrial cancer incidence based on 7 cohort studies, we observed a statistically significant inverse association with low consumption as compared to non-drinkers and a higher risk associated with 2 drinks or more per day.

In the meta-analysis of diabetes and endometrial cancer, based on 16 studies, we found that diabetes was significantly associated with an increased risk of endometrial cancer (summary RR 2.10 95% CI 1.75-2.53). The meta-analysis of type 1 diabetes and endometrial cancer was based on three studies and also found a significant positive association.

In conclusion, our results indicate that dietary factors related to insulin resistance and hyperinsulinemia as well as diabetes may play an important role in the development of endometrial cancer. Hyperinsulinemia may stimulate proliferation of endometrial cells both through insulin-like growth factors and by increased levels of unbound estrogens.
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<thead>
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<th>Description</th>
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<tr>
<td>BMI</td>
<td>Body Mass Index</td>
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<tr>
<td>CI</td>
<td>Confidence Interval</td>
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<td>GI</td>
<td>Glycemic Index</td>
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<td>GH</td>
<td>Growth Hormone</td>
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<td>GL</td>
<td>Glycemic Load</td>
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<tr>
<td>IGF</td>
<td>Insulin-like Growth Factor</td>
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<td>IGFBP</td>
<td>Insulin-like Growth Factor Binding Protein</td>
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<tr>
<td>MET</td>
<td>Metabolic Equivalent</td>
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<tr>
<td>OC</td>
<td>Oral Contraceptives</td>
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<td>OR</td>
<td>Odds Ratio</td>
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<td>PA</td>
<td>Physical Activity</td>
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<td>PMH</td>
<td>Post-Menopausal Hormones</td>
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<td>RR</td>
<td>Relative Risk</td>
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<td>SHBG</td>
<td>Sex Hormone Binding Globulin</td>
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<td>SNP</td>
<td>Single Nucleotide Polymorphisms</td>
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<td>SMC</td>
<td>Swedish Mammography Cohort</td>
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</table>
INTRODUCTION

Endometrial cancer is the fourth most common cancer among women in westernized countries and the eight most common cancer type worldwide. The incidence of endometrial cancer is increasing and large differences in incidence rates between countries can be found.

This difference in incidence suggests that lifestyle factors may be important for the risk of developing endometrial cancer. Diet has also been suspected to be relevant in cancer development. Changes in diet and lifestyle could thus play an important role in the prevention of endometrial cancer.

Figure 1.
Age-standardized incidence rate of endometrial cancer per 100 000

Over the years the evidence that hyperinsulinemia, in the context of insulin resistance, is associated with carcinogenesis has been accumulating. Epidemiologic studies have observed an elevated risk of endometrial cancer in relation to obesity and physical inactivity, the major modifiable determinants of insulin resistance, hyperinsulinemia, and diabetes. Dietary factors such as coffee, quality and quantity of carbohydrates and alcohol have also been shown to affect insulin sensitivity and insulin levels.

In light of the above observation, we aimed to examine these dietary insulin-related factors in the etiology of endometrial cancer and performed three studies analyzing the association between risk of endometrial cancer and coffee, carbohydrates and alcohol in a population-based cohort of over 60 000 women in the Swedish Mammography Cohort.

Furthermore, in order to provide more precise point estimates of the associations between alcohol consumption and endometrial cancer incidence as well as diabetes and endometrial cancer we performed two meta-analyses examining these associations.
ENDOMETRIAL CANCER

Incidence and trends

Around 1300 women are diagnosed with endometrial cancer in Sweden every year, with an incidence of 29.3 per 100 000, which makes it the fourth most common cancer among women in Sweden\(^1\) (the eighth worldwide\(^2\)). The incidence is ten times higher in North America and Europe compared to less developed countries, the lowest rates can be found in Asia and India, an increase in the incidence is observed when life expectancy rises\(^3\).

Figure 2.
Age-standardized incidence of endometrial cancer per 100 000 per age group during 1987-2007 in Sweden\(^4\)

Incidence of endometrial cancer per 100 000 during 1987-2007 in Sweden\(^4\)
The most common way of treatment is surgical removal of the uterus and ovaries, in certain instances the patients also requires radiation therapy. If the uterus for some reason is not surgically removed then radiation in combination with cytostatics and hormones are used\(^1\).

Endometrial cancer often leads to symptoms (such as abnormal bleedings) at early stages, and therefore can be diagnosed early. The prognosis for survival is high at least in westernized countries; the 5-year survival rate in Sweden is over 80\%\(^1\).

**Histopathology**

The endometrium is the lining of the uterus, subject to cyclic changes during the fertile years in women. Endometrial cancer is the most common cancer of the uterine body (corpus uteri).

**Figure 3.**

Anatomy of the uterus

Majority (80\%) of endometrial cancers are endometrioid adenocarcinoma histological type, followed by seropapillary adenocarcinoma, clear-cell adenocarcinoma and endometrioid adenocarcinoma with squamous differentiation \(^3\).

Some authors have argued that endometrial cancer can be divided into two different diseases: Type I or endometroid and Type II or non-endometroid (which includes serous adenocarcinoma, clear-cell adenocarcinoma and squamous carcinoma). Type I mainly occurs in association with hyperplasia and is hypothesized to be affected by unopposed estrogen stimulation. Type II may develop without hyperplasia and thus estrogenic stimulation is not likely to be as important \(^3\). Most Type II endometrial cancers are associated with atrophy, tend to metastasize and have a less favorable prognosis. Unfortunately most studies do not distinguish between these tumor subtypes. This thesis focuses (when possible) on the most common type (endometrioid adenocarcinoma) which is referred to as endometrial cancer.
**Risk factors**

**Age**
In Sweden, the incidence of endometrial cancer rises 5-10 years before menopause until age 75-80, and then declines. The vast majority of the cases are diagnosed after the age of 55\(^1\).

**Estrogen and progesterone**
In both men and women, sex steroid hormones are essential for growth and differentiation as well as functioning of many tissues. Estrogens are mainly produced by the ovaries in premenopausal women. Progesterone is produced by the ovaries as well as adrenal glands and in the brain. A dramatic decline in the ovarian production of estrogen and progesterone is apparent in menopausal women wherein the mayor synthesis of estrogen is observed by peripheral aromatization of androstenedione within adipose tissue\(^5\).

Estrogen and progesterone regulate the growth and differentiation of the endometrium. Estrogen stimulates proliferation of the tissue, while progesterone stimulates differentiation and counteracts the effect of estrogen\(^6\). Over the years, it has become clear that estrogen unopposed by progesterone is the main factor influencing endometrial cancer risk, the theory is known as the unopposed estrogen hypothesis\(^7\). Indeed, each of the reproductive factors that influence long-term exposure to high estrogen and low progesterone levels, such as early age at menarche, late age at menopause, nulliparity, no use of oral contraceptives, and use of unopposed hormone replacement therapy, have been shown to associate with an increased risk of endometrial cancer\(^8-26\).

Sex Hormone Binding Globulin (SHBG) is a globulin that is mainly produced by the liver, and is known to specifically bind sex hormones e.g. estrogen and testosterone in circulation. In general, unbound fractions of hormones are believed to determine the actual biologic activity. The amount and distribution of body fat is clearly inversely associated with blood SHBG concentrations. Studies have shown that SHBG levels are more closely related to abdominal fatness than to overall obesity\(^27\).

**Body mass**
Obesity in adulthood has consistently been associated with an increased risk of endometrial cancer among both pre- and postmenopausal women\(^27\) (Figure 4). Body fatness has been judged as a convincing risk factor according to the World Cancer Research Fund (WCRF) and American Institute for Cancer Research (AICR) expert panel\(^2\). The proportion of endometrial cancer attributable to obesity in Europe has been estimated to 39%\(^28\).

This association has in part been ascribed to increased estrogen levels in obese women. Body mass modulates hormone levels through two mechanisms; 1) inducing an excess of circulating endogenous estrogens due to an increased estrogen production from aromatization of androgen in peripheral fat tissue\(^29-31\), and/or 2) decreasing production of SHBG\(^32\). However, one primary proposed explanation theorizes that high adiposity decreases progesterone levels through increasing the numbers of anovulatory cycles\(^33\). Obesity is also associated with insulin resistance and hyperinsulinemia\(^34-36\), which may increase endometrial cancer risk through estrogenic or growth factor pathways.
Figure 4.
Meta-analysis of the association between body mass index and endometrial cancer,
WCRF/AICR 2007

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Relative risk (95% CI)</th>
</tr>
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<tbody>
<tr>
<td>Ewertz 1984</td>
<td>1.25 (0.93–1.70)</td>
</tr>
<tr>
<td>Baanders-van Haelwijn 1985</td>
<td>1.71 (0.83–3.50)</td>
</tr>
<tr>
<td>Tornberg 1994</td>
<td>1.54 (1.33–1.78)</td>
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<tr>
<td>Tulunnius 1997</td>
<td>1.31 (1.07–1.61)</td>
</tr>
<tr>
<td>Bernstein 1999</td>
<td>1.39 (1.15–1.69)</td>
</tr>
<tr>
<td>Calle 2003</td>
<td>1.40 (1.29–1.51)</td>
</tr>
<tr>
<td>Folsom 2003</td>
<td>1.76 (1.58–1.96)</td>
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<tr>
<td>Furberg 2003</td>
<td>1.59 (1.21–2.09)</td>
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<tr>
<td>Jonsson 2003</td>
<td>1.85 (1.49–2.33)</td>
</tr>
<tr>
<td>Schouten 2004</td>
<td>1.84 (1.48–2.30)</td>
</tr>
<tr>
<td>Kuriyama 2005</td>
<td>1.63 (0.94–2.82)</td>
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<td>Lacey 2005</td>
<td>1.07 (1.00–1.14)</td>
</tr>
<tr>
<td>Repp 2005</td>
<td>1.48 (1.29–1.71)</td>
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<td>Silvera 2005</td>
<td>1.75 (1.56–1.96)</td>
</tr>
<tr>
<td>Lukanova 2006</td>
<td>1.85 (1.33–2.57)</td>
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<tr>
<td>Summary estimate</td>
<td>1.52 (1.35–1.72)</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Case control</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elwood 1977</td>
<td>1.34 (1.10–1.63)</td>
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<tr>
<td>La Vecchia 1992</td>
<td>1.99 (1.62–2.46)</td>
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<tr>
<td>Ewertz 1988</td>
<td>1.57 (1.19–2.08)</td>
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<tr>
<td>Cusimano 1989</td>
<td>1.35 (0.98–1.88)</td>
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<tr>
<td>Zhang 1989</td>
<td>1.63 (1.29–2.05)</td>
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<tr>
<td>Austin 1991</td>
<td>1.36 (1.15–1.60)</td>
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<tr>
<td>Levi 1993</td>
<td>1.38 (1.12–1.71)</td>
</tr>
<tr>
<td>Shu 1993</td>
<td>1.43 (1.07–1.91)</td>
</tr>
<tr>
<td>Swanson 1993</td>
<td>1.25 (1.07–1.47)</td>
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<td>Olson 1995</td>
<td>1.76 (1.41–2.20)</td>
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<tr>
<td>Parazzini 1995</td>
<td>1.59 (1.44–1.76)</td>
</tr>
<tr>
<td>Gruber 1996</td>
<td>1.73 (1.57–1.91)</td>
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<tr>
<td>Kalandidhi 1996</td>
<td>1.93 (1.48–2.51)</td>
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<tr>
<td>Goodman 1997</td>
<td>1.99 (1.62–2.44)</td>
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<td>Geraci 1998</td>
<td>1.47 (0.96–2.24)</td>
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<td>Hachisuga 1998</td>
<td>1.45 (1.17–1.81)</td>
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<td>Hirose 1999</td>
<td>1.65 (1.18–2.29)</td>
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<td>Bead 2000</td>
<td>1.34 (1.06–1.69)</td>
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<tr>
<td>Salazar-Martinez 2000</td>
<td>1.44 (1.09–1.90)</td>
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<td>Weiderpass 2000</td>
<td>1.69 (1.50–1.89)</td>
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<tr>
<td>Newcomer 2001</td>
<td>1.58 (1.44–1.74)</td>
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<td>Petridou 2002</td>
<td>2.12 (1.37–3.27)</td>
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<tr>
<td>Augustin 2003</td>
<td>1.23 (1.08–1.54)</td>
</tr>
<tr>
<td>Horn-Ross 2003</td>
<td>1.16 (1.08–1.25)</td>
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<tr>
<td>Augustin 2004</td>
<td>2.10 (1.27–3.48)</td>
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<tr>
<td>Trethem-Dietz 2005</td>
<td>1.69 (1.54–1.84)</td>
</tr>
<tr>
<td>Xu 2005</td>
<td>1.78 (1.54–2.06)</td>
</tr>
<tr>
<td>Okamura 2006</td>
<td>1.74 (1.02–2.97)</td>
</tr>
<tr>
<td>Summary estimate</td>
<td>1.56 (1.45–1.66)</td>
</tr>
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</table>

Relative risk per 5 kg/m²
A number of studies\textsuperscript{37-45} have investigated abdominal fatness, most studies have found an increased risk with increased abdominal fatness. Many of the mechanisms thought to be important in the etiology of endometrial cancer such as increased levels of estrogen and decreased insulin sensitivity are associated with abdominal fatness independently of overall fatness\textsuperscript{46}.

\textit{Attained height}

Several studies\textsuperscript{47, 48} have investigated adult attained height, showing inconsistent results, but in general an increased risk for endometrial cancer with greater height has been reported. The proposed mechanisms include early life nutrition, hormone profiles and the rate of sexual maturation\textsuperscript{48}.

\textit{Insulin resistance and diabetes}

Insulin controls the uptake, synthesis and use of glucose in the body. Insulin resistance is a state of reduced responsiveness of liver, muscle and adipose tissue to insulin, which leads to a rise in blood glucose levels. In extreme cases, insulin resistance may cause glucose intolerance and lead to the development of type 2 diabetes\textsuperscript{49}. Elevated insulin concentrations and decreased glucose tolerance are associated with obesity\textsuperscript{5}. The relationship between body mass index (BMI) and fasting insulin levels is continuous and linear\textsuperscript{27}. Studies have shown that an increase in visceral fat is especially related to the development of insulin resistance. Weight reduction, particularly loss of visceral fat mass, leads to improved insulin sensitivity and to decreased insulin concentrations. Independent of the effect on excess body fat, lack of physical activity may also contribute to the development of insulin resistance\textsuperscript{5}.

Insulin and insulin-like growth factor (IGF), as a function of available energy, are central to the regulation of growth processes. Insulin and IGF-1 also act as regulators of sex-steroids availability by stimulating steroidogenesis while at the same time inhibiting the hepatic synthesis of SHBG. Thus, alterations in levels of insulin or in IGF-1 bioactivity provide an important link between energy balance, physical activity and levels of bioavailable sex hormones\textsuperscript{27}.

Hyperinsulinemia may increase levels of free estrogen through decreasing concentrations of circulating SHBG\textsuperscript{50, 51}. Furthermore, hyperinsulinemia through decreasing levels of insulin-like growth factor binding protein-1 (IGFBP-1) and IGFBP-3 increases circulating free IGF-1, which by binding and activating IGF-1 receptors in the endometrium may stimulate cell proliferation\textsuperscript{52-56}.

A number of epidemiological studies have reported on associations between diabetes and endometrial cancer, see Table 1-3 in paper V.
**Adiponectin**

Adiponectin is an adipose tissue derived endogenous insulin sensitizer which is decreased in obesity\(^5^7\). It has been reported that hyperinsulinemia is closely associated with lower circulating levels of adiponectin\(^5^8\). It has also been shown that low adiponectin levels are associated with low levels of physical activity\(^5^9, 6^0\), higher levels of body fat and visceral tissue \(^3^6\), higher concentrations of circulating estradiol\(^6^1\), and increased endometrial cancer risk\(^6^2-6^5\).

**Physical activity**

A number of epidemiologic studies have reported on associations between different physical activities and incidence of endometrial cancer \(^4^5, 4^7, 6^6-8^4\). Most studies have shown some aspect of physical activity to be inversely associated with endometrial cancer risk. Physical activity has been judged as a “probable” factor to be protective against endometrial cancer by the WCRF/AICR report 2007. The proposed mechanism for the protective effect relates to lower levels of endogenous estrogen among physically active women\(^8^5, 8^6\). Physical inactivity is a major determinant of body weight and may shift the body composition towards more body fat and visceral tissue. Physical inactivity has also been shown to affect insulin resistance and hyperinsulinemia\(^8^7, 8^8\) not only through obesity but also directly. Physical activity has been shown to promote insulin sensitivity\(^8^9, 9^0\).

**Diet**

According to the WCRF/AICR there is a suggestion that non-starchy vegetables decrease risk of endometrial cancer and that red meat consumption increases the risk of this disease. Other dietary factors such as; cereals, fiber, fruit, pulses, soya, poultry, fish, eggs, dairy products, fat, protein, retinol, vitamin C, vitamin E, beta-carotene, and energy, are insufficiently studied to permit any conclusions\(^2\).

**Vegetables**

One cohort study\(^9^1\) and several case-control studies \(^4^5, 7^2, 9^2-9^9\) have investigated an association between consumption of vegetables and endometrial cancer risk. Most studies showed decreased risk with increased intake. Many different plant foods are represented and many factors might contribute to the observed decreased risk.

**Meat**

One cohort study\(^1^0^0\) and several case-control studies \(^4^5, 9^2, 9^7-9^9, 1^0^1, 1^0^2\) have investigated the association between red meat and endometrial cancer. Most studies observed an increased risk with high intake of red meat. There are several possible mechanisms for this association including known carcinogenic substances such as N-nitroso compounds, heterocyclic amines and polycyclic aromatic hydrocarbons. Red meat also contains haem-iron which might lead to production of free radicals\(^1^0^3, 1^0^4\).
Carbohydrates, glycemic index and glycemic load

Diet can influence insulin levels, especially among individuals who are insulin resistant due to other factors. Studies on carbohydrate intake and endometrial cancer have been inconsistent but mostly show non-significant results. Glycemic index as a concept was developed as a measure of the glycemic response induced by the carbohydrates in different foods. Glycemic load is defined as the product of foods’ glycemic index and their carbohydrate content. Glycemic load was introduced to give an overall measure of the postprandial glycemia and insulin demand. High glycemic index and load have been associated with higher levels of glycosilated haemoglobin, higher C-peptide levels, and lower levels of adiponectin. Moreover, it has also been shown that a low glycemic index diet may increase SHBG levels and decrease estrogen and testosterone levels.

Only one case-control and three cohort studies have evaluated glycemic index and glycemic load in relation to risk of endometrial cancer. Only the case-control study observed a statistically significant increased risk of endometrial cancer with high glycemic index diet. Neither of the cohort studies found an overall increased risk for glycemic index or load. However, two cohorts observed a statistically significant increased risk of endometrial cancer in relation to glycemic load among obese women.

A recent meta-analysis on glycemic index, glycemic load and endometrial cancer (including our study in paper II) reported a summary relative risk of 1.20 (95% CI 1.06-1.37) for high glycemic load consumers which was further elevated among obese women; no association was observed between high glycemic index diet and endometrial cancer.
Table 1.
Characteristics of epidemiologic studies of coffee and endometrial cancer incidence*

<table>
<thead>
<tr>
<th>Authors, year, country</th>
<th>Case/Cohort/Controls</th>
<th>RR (95% CI) †</th>
<th>Controlled variables</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cohort studies</strong></td>
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<td></td>
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</tr>
<tr>
<td>Friberg, 2009, Sweden</td>
<td>677/60 634</td>
<td>0.75 (0.58-0.97)</td>
<td>Age, BMI, smoking</td>
</tr>
<tr>
<td>Shimazu, 2008, Japan</td>
<td>117/53 724</td>
<td>0.38 (0.16-0.91)</td>
<td>Age, BMI, smoking, study area, menopausal status, age at menopause, parity, exogenous hormone use, green vegetables, beef, pork, green tea</td>
</tr>
<tr>
<td>Stensvold, 1994, Norway</td>
<td>84/21 238</td>
<td>0.8 (NS)</td>
<td>Age, smoking, county of residence.</td>
</tr>
<tr>
<td><strong>Case-control studies</strong></td>
<td></td>
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<tr>
<td>Bravi, 2009, Italy</td>
<td>454/908</td>
<td>0.50 (0.29-0.86)</td>
<td>Age, BMI, center, year, education, total energy, diabetes, age at menarche, parity, OC, PMH, menopausal status.</td>
</tr>
<tr>
<td>McCann, 2008, USA</td>
<td>541/541</td>
<td>0.71 (0.49-1.03)</td>
<td>Age, BMI, smoking, PMH, OC, education, menopausal status, tea.</td>
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<tr>
<td>Koizumi, 2008, Japan</td>
<td>107/214</td>
<td>0.4 (0.2-0.9)</td>
<td>Age, BMI, smoking, education, age at menarche, pregnancies, OC, diabetes, total calories.</td>
</tr>
<tr>
<td>Hirose, 2007, Japan</td>
<td>229/12 425</td>
<td>0.41 (0.19-0.87)</td>
<td>Age, BMI, smoking, year, motivation for consultation, parity, age at first delivery, drinking, type of breakfast, fondness of salty and fatty foods, fruit, vegetables, beef, fish, carrot and exercise.</td>
</tr>
<tr>
<td>Petridou, 2002, Greece</td>
<td>84/84</td>
<td>0.39 (0.17-0.93)</td>
<td>Age, BMI, current smoking, education, height, age at menarche, menopausal status, pregnancies and abortions, alcohol, cholecystectomy</td>
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<tr>
<td>Terry, 2002, Sweden</td>
<td>709/2887</td>
<td>0.7 (0.5-1.0)</td>
<td>Age, BMI, smoking, physical activity, diabetes, fatty fish, total food, fruit and vegetables, fruit, brassica, non-brassica, dairy, high fiber, legumes, meat.</td>
</tr>
<tr>
<td>Levi, 1993, Italy, Switzerland</td>
<td>274/572</td>
<td>1.22 (NS)</td>
<td>Age, study center</td>
</tr>
</tbody>
</table>

*RR=relative risk; CI=confidence interval; NS=non-significant; BMI=body mass index; PMH=postmenopausal hormone use; OC=oral contraceptive use
†The measure of RR is a rate ratio for cohort studies and odds ratios (OR) for case-control studies.
Coffee

Coffee consumption has been reported to improve insulin sensitivity\textsuperscript{124} and to decrease the risk of developing diabetes\textsuperscript{125}. Therefore an association between coffee consumption and endometrial cancer risk, possibly modified by body weight, is biologically plausible. Endometrial cancer risk in relation to coffee consumption has been studied in two prospective studies (a Japanese study showing statistically significant decrease in risk\textsuperscript{126}, and one Norwegian study showing a non-significant decrease in risk\textsuperscript{127}) as well as in eight case-control studies (five showing statistically significant decreased risk with increasing consumption of coffee\textsuperscript{92, 128-131}, one observing a non-significant decreased risk\textsuperscript{95} and two a non-significant increase in risk\textsuperscript{45, 97}) (Table 1). A recent meta-analysis on coffee and endometrial cancer risk reported a summary RR of 0.92 (95% CI 0.88-0.96) per cup of coffee/day among case-control studies\textsuperscript{132}.

Alcohol

A number of studies have investigated a potential relationship between alcohol and incidence of endometrial cancer (Table 2 and 3). Epidemiologic studies have not been entirely consistent. While most of these have not shown any significant association between alcohol consumption and endometrial cancer risk\textsuperscript{10, 45, 97, 98, 105, 133-142}, some have reported an increased risk\textsuperscript{68, 99, 143, 144} and a case-control study indicated a decreased risk\textsuperscript{145}.

Other dietary factors

The potential association between acrylamide and endometrial cancer has been investigated in the Swedish Mammography Cohort not showing any association\textsuperscript{146} as well as in a Dutch cohort study showing an elevated risk for endometrial cancer with higher intake of acrylamide\textsuperscript{147}.

Cadmium has also been investigated in the Swedish Mammography Cohort\textsuperscript{148}, cadmium is hypothesized to exert estrogen mimicking effects and could thus influence the risk of endometrial cancer. An increased risk was observed when comparing women with a high cadmium intake to those with a low intake.

Cigarette smoking

A protective effect of cigarette smoking on endometrial cancer risk was suggested as early as 1980\textsuperscript{149}. Since then a number of epidemiologic studies have confirmed the reduced risk\textsuperscript{15, 137, 140, 149-151}. The inverse association of cigarette smoking with endometrial cancer risk may relate to the fact that female smokers have similar hormonal characteristics as those who are relatively estrogen deficient. Since smoking is related to an earlier age at menopause and an increased risk of osteoporosis, both of which indicate less exposure to endogenous estrogens, it has been hypothesized that smoking acts by diminishing estrogenic effects\textsuperscript{152}.
<table>
<thead>
<tr>
<th>Authors, country, year</th>
<th>Case/Cohort</th>
<th>RR (95% CI) †</th>
<th>Controlled variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allen, United Kingdom, 2009</td>
<td>4118/1280296</td>
<td>0.99 (0.85-1.16)</td>
<td>Age, BMI, smoking, PMH, OC, physical activity, socioeconomic status, region of residence</td>
</tr>
<tr>
<td>Friberg, Sweden, 2009</td>
<td>687/61226</td>
<td>1.09 (0.71-1.68)</td>
<td>Age, BMI, smoking, PMH, OC, parity, age at menarche, age at menopause, diabetes, education, energy</td>
</tr>
<tr>
<td>Setiawan, USA, 2008</td>
<td>324/41574</td>
<td>2.01 (1.30-3.11)</td>
<td>Age, BMI, smoking, PMH, OC, parity, age at menarche, age at menopause, diabetes, hypertension, vigorous exercise, education, race, year, study center</td>
</tr>
<tr>
<td>Loerbroks, Netherland, 2007</td>
<td>254/1901</td>
<td>1.78 (0.88-3.6)</td>
<td>Age, BMI, smoking, OC, parity, age at first child, age menopause, hypertension, physical activity</td>
</tr>
<tr>
<td>Jain, Canada, 2000</td>
<td>221/56837</td>
<td>1.00 (0.67-1.5)</td>
<td>Age, BMI, smoking, PMH, OC, live births, age menarche, education, energy</td>
</tr>
<tr>
<td>Terry, Sweden, 1999</td>
<td>117/11659</td>
<td>1.1 (0.5-2.4)</td>
<td>Age, weight, parity, physical activity</td>
</tr>
<tr>
<td>Gapstur, USA, 1993</td>
<td>160/25170</td>
<td>1.0 (0.7-1.6)</td>
<td>Age, BMI, PMH, parity, age menopause</td>
</tr>
</tbody>
</table>

*RR=relative risk; CI=confidence interval; BMI=body mass index; PMH=postmenopausal hormone use; OC=oral contraceptive use
†The measure of RR is a rate ratio (hazard ratio) in all studies
Table 3. Characteristics of case-control studies of alcohol and endometrial cancer incidence*

<table>
<thead>
<tr>
<th>Authors, country, year</th>
<th>No. of cases/controls</th>
<th>RR (95% CI)</th>
<th>Controlled variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hosono, Japan, 2008</td>
<td>148/1468</td>
<td>0.47 (0.14-1.58)</td>
<td>Age, BMI, smoking, PMH, OC, parity, menstrual status, age at menarche, duration menstruation, diabetes, hypertension, regular exercise, flushing after drinking</td>
</tr>
<tr>
<td>Weiderpass, Sweden, 2001</td>
<td>709/3368</td>
<td>0.92 (0.70-1.20)</td>
<td>Age, BMI, smoking, PMH, OC, parity, age last birth, age menopause, diabetes</td>
</tr>
<tr>
<td>Newcomb, USA, 1997</td>
<td>739/2313</td>
<td>1.27 (0.78-2.07)</td>
<td>Age, relative weight, smoking, PMH, parity, education,</td>
</tr>
<tr>
<td>Goodman, USA, 1997</td>
<td>332/511</td>
<td>0.9 (0.6-1.4)</td>
<td>Age, BMI, PMH, OC, pregnancy history, diabetes, ethnicity</td>
</tr>
<tr>
<td>Kalandidi, Greece, 1996</td>
<td>145/298</td>
<td>0.7 (0.4-1.3)</td>
<td>Age, BMI, Smoking, PMH, OC, energy</td>
</tr>
<tr>
<td>Parazzini, Italy, 1995</td>
<td>726/2123</td>
<td>1.6 (1.2-2.2)</td>
<td>Age, BMI, Smoking, PMH, OC, parity, age menopause, diabetes, hypertension, education</td>
</tr>
<tr>
<td>Swanson, USA, 1993</td>
<td>400/297</td>
<td>0.82 (0.53-1.26)</td>
<td>Age, BMI, body fat distribution, smoking, OC, age menarche, education</td>
</tr>
<tr>
<td>Shu, China, 1993</td>
<td>268/268</td>
<td>1.2 (0.6-2.6)</td>
<td>Age, BMI, pregnancies</td>
</tr>
<tr>
<td>Levi, Switzerland and Italy, 1993</td>
<td>274/572</td>
<td>1.19 (NA)</td>
<td>Age, energy, study center</td>
</tr>
<tr>
<td>Austin, USA, 1993</td>
<td>103/236</td>
<td>0.6 (0.3-1.3)</td>
<td>Age, BMI, smoking, PMH</td>
</tr>
<tr>
<td>Kato, Japan, 1989</td>
<td>239/8920</td>
<td>0.5 (0.2-1.7)</td>
<td>Age, smoking, family breast cancer, occupation, residence, marital status</td>
</tr>
<tr>
<td>Webster, USA, 1989</td>
<td>351/2247</td>
<td>0.55 (0.35-0.90)</td>
<td>Age, BMI, smoking, PMH, OC</td>
</tr>
<tr>
<td>Cusimano, Italy, 1989</td>
<td>68/237</td>
<td>1.31 (0.73-2.34)</td>
<td>Unadjusted</td>
</tr>
<tr>
<td>Williams, USA, 1977</td>
<td>NA</td>
<td>0.63 (NA)</td>
<td>Age, smoking, race</td>
</tr>
</tbody>
</table>

NA = data were not available
* RR=relative risk; CI=confidence interval; BMI=body mass index; PMH=postmenopausal hormone use; OC= oral contraceptive use
Genetic susceptibility

Data indicate that endometrial cancer may occur in genetically susceptible women; 5% of the cases has been estimated to be hereditary. Data on familiar aggregation reflecting clustering of either sporadic or hereditary cases is however scarce.

The study of genetic single nucleotide polymorphisms (SNPs, genetic variations defined as single base substitutions with a frequency greater than 1% in the population) may explain differences in cancer susceptibility and be used to create more effective cancer prevention strategies. SNPs in functionally critical genes have been postulated to be risk factors. The genes may, for example, be involved in DNA damage repair, steroid metabolism, carcinogen metabolism, cell cycle control, apoptosis and steroid receptor activation.

Given the fundamental role of sex hormones in endometrial carcinogenesis, studies of genetic susceptibility have focused on the influence of polymorphisms in estrogen receptors and genes involved in estrogenic metabolism, such as the regions coding the CYP-enzymes. However, results are still limited and there is a need for confirmatory studies.

Endometrial cancer would seem to be a useful model for further studies of genetic susceptibility to sex-hormone dependent carcinogenesis.
AIMS

- To evaluate the association between coffee drinking and the risk of endometrial cancer among women in the Swedish Mammography Cohort.

- To evaluate the risk of endometrial cancer associated with glycemic index, glycemic load and carbohydrate intake among women in the Swedish Mammography Cohort.

- To examine the association between alcohol consumption and endometrial cancer incidence in the Swedish Mammography Cohort.

- To quantitatively summarize the evidence, using meta-analysis, on the association between alcohol and incidence of endometrial cancer.

- To quantitatively summarize the accumulated evidence, using meta-analysis, on the association between type 2 diabetes and incidence of endometrial cancer and to evaluate the association between type 2 diabetes and endometrial cancer mortality as well as type 1 diabetes and endometrial cancer.
SUBJECTS AND METHODS

THE SWEDISH MAMMOGRAPHY COHORT STUDY - PAPER I-III

Cohort population

Figure 5.
Study population

Source population
All women (90,303, born 1914-48) and living in Uppsala county (n=48,517) and (1917-48) in Västmanland (n=41,786) received an invitation to participate in a mammography screening program between March 1987 and December 1990. Together with the invitation the women also received a questionnaire.

Questionnaire 1
66,651 (74%) women returned a completed 1st questionnaire

Non-responders (n=23,652)
Excluded (n=5,188) due to incorrect or missing identification numbers, dates missing on the questionnaire or for moving out of the study area or for death, outside the age-range 40-76 years, extreme energy intake, cancer diagnosis prior to baseline.

Hysterectomy (n=237)

Missing data on coffee (n=592)

Paper I, Coffee (n=60,634)
677 cases (1987-2007)

Paper II, Carbohydrates (n=61,226)
608 cases (1987-2005)

Paper III, Alcohol (n=61,226)
689 cases (1987-2007)

Questionnaire 2
Updated information, in 1997 an extended questionnaire was sent to 56,030 members of the cohort who were alive and still living in the study area, 70% responded.
Exposure assessment, case ascertainment and follow up.

From 1987 to 1990, all women who lived in the Uppsala County of central Sweden and were born in 1914-1948 (n=48,517) and all women who lived in the adjacent Västmanland County (n=41,786) and were born in 1917-1948 received an invitation, mailed together with a questionnaire, to participate in a free mammography screening program. A total of 66,651 women (74%) returned a completed questionnaire on diet including carbohydrate intake and coffee and alcohol drinking, as well as information about weight, height, parity and education.

In 1997, a second questionnaire was sent to all 56,030 cohort members who were still living in the study area; the second questionnaire was extended with information about medical history including diabetes and hypertension, age at menarche, history of oral contraceptive use, age at menopause, postmenopausal hormone use, and lifestyle factors, such as cigarette smoking history, physical activity history and use of dietary supplements; 39,227 (70%) women returned a completed questionnaire. Women who did not answer the second questionnaire were on average older, less educated, and had a slightly higher BMI compared to women who did answer the second questionnaire.

Data on diet was collected at baseline 1987-90 and in 1997 by use of a self-administered food-frequency questionnaire that included 67 and 96 food items commonly consumed in the study population, respectively. The women were asked to report how often on average they consumed different food items during the last six months; the women could choose one from 8 pre-specified frequencies ranging from “never or seldom” to “4 times per day or more” (Figure 6). In the 1997 questionnaire there was an open ended question on how many cups of coffee per day or per week the women consumed during the last year. This questionnaire also included a question on usual amount of beer, wine and/or liquor consumed on each occasion. We used age-specific (<53, 53-65, >65 years) serving sizes that were based on mean values obtained through evaluation of randomly chosen women from SMC who weighed and recorded food intake for four 1-week periods (Wolk A: unpublished data). The correlation coefficients between baseline food frequency questionnaires and weighted records was; 0.6 for coffee drinking; 0.5 for carbohydrate intake; and 0.9 for alcohol consumption.

The average daily intake of alcohol was computed by multiplying the frequency of the consumption of beer, wine and/or liquor by the amount in each of these alcoholic beverages. Total alcohol intake was the sum of alcohol for all three types. The amount was then converted into grams of alcohol per day (volume % x 0.8 = gram). We expressed alcohol consumption as number of drinks per day by considering 13 grams of alcohol to be equivalent to one drink. Thirteen grams of alcohol correspond to approximately 330 ml of beer, 150 ml of wine, or 45 ml of liquor.
Figure 6.
Example on page with questions from the food frequency questionnaire used in the SMC at baseline 1987-1990 including questions on coffee and alcoholic beverages.

<table>
<thead>
<tr>
<th>Food Item</th>
<th>Never/ Seldom</th>
<th>1-3 month</th>
<th>1 week</th>
<th>2-3 week</th>
<th>4-6 week</th>
<th>1 day</th>
<th>2-3 day</th>
<th>4 day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citrus fruits</td>
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<td>Banana</td>
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<td>Juice</td>
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<tr>
<td>Oat meal, gruel, hot cereal</td>
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<tr>
<td>Cold cereal, müsli</td>
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<tr>
<td>Pancakes, waffles</td>
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<td>Rice</td>
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<td>Spaghetti</td>
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<tr>
<td>Brown beans, pea soup</td>
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<tr>
<td>Meat, whole pieces</td>
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<tr>
<td>Meat, stews, casseroles</td>
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<tr>
<td>Bacon</td>
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<tr>
<td>Minced meat</td>
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<tr>
<td>Sausage &amp; sausage dishes</td>
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<tr>
<td>Cold cuts</td>
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<tr>
<td>Blood pudding/sausage</td>
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<tr>
<td>Liver, kidney</td>
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<td>Poultry</td>
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<tr>
<td>Eggs, scrambled eggs</td>
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<tr>
<td>Salmon, mackerel, herring</td>
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<tr>
<td>Other fish</td>
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<tr>
<td>Sea food (shrimp, mussels, crab)</td>
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<tr>
<td>Chips, popcorn, nuts, cheese doodles</td>
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<tr>
<td>Rolls, crackers, cookies</td>
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<tr>
<td>Ice cream</td>
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<td>Sweet soup</td>
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<td></td>
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<tr>
<td>Jam, marmalade</td>
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<tr>
<td>Lemonade</td>
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<td>Sodas</td>
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<tr>
<td>Candy</td>
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<tr>
<td>Chocolate</td>
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<td>Sugar</td>
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<tr>
<td>Coffee</td>
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<tr>
<td>Tea</td>
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<tr>
<td>Beer, 0.5% alcohol</td>
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<tr>
<td>Beer, 2.8% alcohol</td>
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<tr>
<td>Beer, 4.5% alcohol</td>
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<tr>
<td>Wine</td>
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</tr>
<tr>
<td>Hard liquor, 40% alcohol</td>
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</tbody>
</table>
Glycemic load was calculated by multiplying the carbohydrate content (grams per serving) of each food by its glycemic index and multiplying that product by the frequency of consumption and adding the values from all foods. Glycemic load represents the quality and quantity of carbohydrates, each unit of glycemic load represents the equivalent of 1g of carbohydrates from white bread. Glycemic index for different foods were obtained through published tables\textsuperscript{154}. We calculated the glycemic index for each woman by dividing the glycemic load by total carbohydrate intake which represents the overall quality of carbohydrates. Carbohydrate intake, glycemic index and load were all energy adjusted by using the residual method\textsuperscript{155}.

Body mass index was calculated as weight in kg divided with the square of the height in meters (kg/m\(^2\)); the validity for self-reported weight and height as compared to measurements in Swedish women has been studied and the Pearson correlation coefficients were r = 0.9 and 1.0 respectively\textsuperscript{156}.

Education was assessed with six questions ranging from 6 years of basic education to university studies. Diabetes was self-reported on the second questionnaire and assessed with the question “have you ever been diagnosed with diabetes”; for women with diabetes who were hospitalized we also obtained information by linkage of the cohort to the Swedish In-patient Register.

Information on physical activity was based on six questions in the 1997-questionaire about physical activity/inactivity during the previous year. We asked for duration of specific activities and we assigned mean MET-values (multiples of the metabolic equivalent MET, kcal/\(\text{kg} \cdot \text{h}\)) based on specific activities within corresponding categories in a physical activity compendium\textsuperscript{157, 158}. For work/occupation there were six predefined types of work, and a question about full time or part-time employment allowed us to assign correct work duration. We predefined the following types of occupational activity: mostly sitting (1.3 MET/h), sitting down more than half the time (1.8 MET/h), mostly standing (2.2 MET/h), doing lifts (2.6 MET/h), a lot of lifts (3.0 MET/h) and heavy labor (3.9 MET/h). For household work and walking/bicycling there were six predefined duration categories for time – home/household work (less than 1 h daily to more than 8 h daily, 2.5 MET/h); walking/bicycling (almost never to more than 1.5 h daily, 3.6 MET/h). For leisure time activity there were 5 predefined duration categories (less than 1 h per week to more than 5 h per week, 5.0 MET/h), and five predefined categories for time spent per day watching TV/sitting (inactive leisure time, less than 1h daily to more than 6 h daily, 1.2 MET/h). There was an additional open ended question about number of hours of sleep per day (0.9 MET/h). We estimated the total activity by adding up the respective products of duration by intensity of specific activities and corrected the self-reported time to 24 h per day, by adding hours (if the total sum was below 24 h) or deleting hours (if the total sum was above 24 h). The correction time was multiplied by the intensity factor 2.0 MET, corresponding to the mean intensity of self-care/walking at home and sitting.

In paper II (carbohydrates) we performed linkage of the cohort with the National Swedish Cancer Register and the Regional Cancer Register through June 30, 2005. In paper I and III (coffee and alcohol) we performed linkage of the cohort with the registries through December 31, 2007. The National Swedish Cancer Register and the Regional Cancer Register, have been estimated to be almost 100% complete\textsuperscript{159}. Furthermore, by linkage with
the nationwide Swedish In-patient Register, we identified women who had a hysterectomy for reasons other than endometrial cancer. Dates of death or migration from the study area were ascertained by linkage with the Swedish Death Register and the Swedish Population Register, respectively. Of the 66,651 women who responded to the first questionnaire in 1987-90, we excluded those with a cancer diagnosis (other than non-melanoma skin cancer) before the study baseline, those with a missing identification number, with ages outside the range 40-76 years, with extreme reported energy intake, and with a history of hysterectomy before entry to the cohort. We only included adenocarcinoma endometrial cancer as cases. After these exclusions 61,226 women aged 40 to 76 years at baseline remained for the main analysis in paper II and III (carbohydrates and alcohol) including 608 cases of endometrial cancer in paper II (carbohydrates) and 687 cases in paper III (alcohol). Furthermore, in paper I (coffee) we excluded women with missing information on coffee consumption (n=592). After these exclusions, 60,634 women at baseline remained for analyses, including 677 endometrial cancer cases.

These studies were approved by the Ethics Committees at the Uppsala University Hospital (Uppsala) and the Karolinska Institutet (Stockholm). Completion of the self-administered questionnaire was considered to imply informed consent to participate in the studies.

**Statistical analysis**

To estimate the risk of endometrial cancer we used Cox proportional hazards models. We calculated person-years of follow-up for each woman from the date of mammography to the date of endometrial cancer diagnosis, the date of a hysterectomy, the date of death from any cause, the date of migration out of the study area during a time period when we only have regional information on cancer incidence (e.g. the last two years of follow-up), or the end of follow-up (June 30, 2005 in paper II (carbohydrates) or December 31, 2007 in paper I and III (coffee and alcohol)), whichever came first. We computed incidence rate ratios by dividing the number of incident cancer cases by the number of person-years of follow-up in each category, stratified by age in months. The rate ratios of endometrial cancer (with 95% confidence intervals) were calculated by dividing the incidence rates among women in the upper categories of intake with women in the lowest category of intake. The data conformed to the proportional hazards assumption. All p-values are 2-sided.

**Paper I, Coffee**

We performed age-adjusted and multivariable analyses. In the main analysis we included coffee consumption from the baseline questionnaire, BMI and smoking. We categorized coffee in three groups according to the distribution in the cohort. We also performed analysis further adjusting for known risk factors and potential confounders such as years of education, age at menopause, age at menarche, oral contraceptive use, postmenopausal hormone therapy, parity, history of diabetes and total energy intake, as well as such foods correlated with coffee drinking as tea and consumption of buns, cookies and cakes. Missing values for any potential confounder were treated as a separate “missing category” in the model.
We also calculated the RR of endometrial cancer (with 95% CI) using updated information on coffee for those answering the second questionnaire, and by using for the time period January 1, 1998 to December 31, 2007 the average coffee consumption from the two questionnaires. In test for linear trend, we used the median value in each category as a continuous variable in the model. To flexibly model and graph the multivariable adjusted rate ratio for coffee consumption and endometrial cancer incidence we used restricted cubic splines (three knot positions)\textsuperscript{161, 162}. We conducted analyses stratifying on BMI (baseline) and physical inactivity (second time period only). We also conducted analyses on diabetics. Statistical significance of interactions was tested by adding an interaction term to the Cox model, simultaneously containing the main variables and age in months. Analyses were performed using SAS and Stata software.

*Paper II, Carbohydrates*

We categorized women into quintiles of carbohydrate intake, glycemic load and glycemic index and calculated the RR of endometrial cancer (with 95% CI). In the main model we adjusted for age and total energy intake. We also performed analysis including other potential confounders but these did not change the results. To test for trend, we assigned the median value to each exposure category and treated this as a continuous variable in the model. Further we performed analyses stratifying on BMI and physical inactivity. Tests for interaction were conducted using likelihood ratio tests. Analyses were performed using SAS software.

*Paper III, Alcohol*

We categorized women into 4 categories of alcohol intake and calculated the RR of endometrial cancer (with 95% CI). Multivariable models were adjusted for age, BMI and smoking. We also calculated the RR of endometrial cancer using updated information on alcohol intake from the second questionnaire, by using for the time period January 1, 1998 to December 31, 2007 the average alcohol intake from the two questionnaires. Possible interactions were tested by adding an interaction term to the model simultaneously containing the main variables and age. Analyses were performed using SAS software.
META-ANALYSES

Alcohol - Paper IV

Search Strategy
We identified studies by a literature search of the Pub-Med and Embase databases (from the beginning of the databases through March 15, 2009) with the following medical subject heading terms and/or text words: “alcohol”, “alcoholic drink”, “liquor”, “beer”, “ethanol”, “endometrial cancer”, “corpus uteri”. We also reviewed reference lists of the identified publications for additional pertinent studies. No language restrictions were imposed.

Figure 7.
Study selection progression in meta-analysis of alcohol and endometrial cancer risk
Data extraction
The data we extracted included publication data (first author, year of publication and country of population), number of exposed and unexposed subjects, follow-up period, risk estimates with confidence intervals and variables controlled for in multivariable models. From each study, we extracted the risk estimates that reflected the greatest degree of control for potential confounders.

Statistical analysis
We examined the relationship between alcohol consumption and endometrial cancer risk based on the relative risks and 95% confidence intervals published in each study.

We first performed a meta-analysis comparing the highest vs. the lowest alcohol consumption categories within the specific studies. The summary RR estimate with its 95% confidence interval was derived with the method of DerSimonian and Laird\textsuperscript{163} by use of the assumption of a random effects model, which incorporated between-studies variability.

We next conducted a dose-response random-effects meta-regression analysis from the correlated natural log of the RRs across categories of alcohol intake\textsuperscript{164, 165}. This method requires that the distribution of cases and non-cases or person-time and the RR with its variance estimate for at least 3 quantitative exposure categories are known. Because the studies included in our meta-analysis used different units to report alcohol consumption (e.g. grams or number of drinks per day or week) we expressed alcohol consumption into drinks per day by considering 13 grams of alcohol to be equivalent to one drink. Thirteen grams of alcohol correspond to approximately 330 ml of beer, 150 ml of wine, or 45 ml of liquor. For each study, the median or mean level of consumption for each category was assigned to each corresponding RR. When the median or mean consumption was not reported, we assigned the midpoint of the upper and lower bound in each category as the average intake. If the upper bound in the highest category was not provided, we assumed that it had the same amplitude as the preceding category. We used restricted cubic splines (three knots) to flexibly model and graph the relative risk for alcohol consumption and endometrial cancer risk\textsuperscript{161}.

In all meta-regression models statistical heterogeneity between studies was evaluated with Cochran’s $Q$ test and the $I^2$ statistic\textsuperscript{166}. $I^2$ is the proportion of total variation contributed by between-study variation. Publication bias was assessed by Egger’s regression asymmetry test\textsuperscript{167}. To investigate potential sources of heterogeneity, we performed a subgroup analysis among studies that adjusted for confounders like smoking and body mass index. We also conducted a sensitivity analysis iteratively excluding each study from the overall dose-response meta-analysis.

Statistical analyses were carried out with Stata software. $P$-values that were less than .05 were considered statistically significant. All statistical tests were two-sided.
Search Strategy
We identified studies by a literature search of Pub-Med and Embase databases (from the beginning of the databases, through January 31, 2007) using the following key words: “diabetes mellitus”, “diabetes”, “endometrial cancer”, “corpus uteri”. We also reviewed reference lists of the identified publications for additional studies.

Figure 8.
Study selection progression in the meta-analysis on diabetes and endometrial cancer risk
**Data extraction**
We extracted the following data: publication date, study design, number of exposed and unexposed subjects, follow-up period, control source, type of diabetes, risk estimates with their corresponding confidence intervals, and variables controlled for by matching or in the multivariable model.

**Statistical Analysis**
We divided the epidemiologic studies that assessed the relationship between diabetes and endometrial cancer risk into three general types according to the measure of relative risk: cohort studies, case-control studies, and cohort studies with an external comparison group. We conducted separate meta-analyses of endometrial cancer incidence and mortality. The measure of effect of interest was the relative risk. Cohort studies that reported standardized incidence/mortality ratio were analyzed separately. Studies reporting an estimate for type 1 diabetes were analyzed separately.

Summary relative risk estimates with their corresponding 95% confidence intervals were derived with the method of DerSimonian and Laird by use of the assumption of a random effects model, which incorporated between-studies variability. We calculated a pooled relative risk and its corresponding 95% confidence interval for relative risk. Statistical heterogeneity between studies was evaluated with Cochran’s Q test and the I² statistic. Publication bias was assessed by constructing a funnel plot, and by Egger’s regression asymmetry test.

In analysis of cohort studies that reported incidence rate ratios and case-control studies, we conducted subgroup meta-analyses to examine potential sources of heterogeneity, including study design, and hospital vs population based case-control studies. All analyses were done using Stata software.
RESULTS

COFFEE - PAPER I
During a mean follow-up time of 17.6 years of 60,634 women in the cohort (1,066,348 person-years) 677 incident adenocarcinoma endometrial cancer cases were diagnosed. The mean age at diagnosis of endometrial cancer was 67.3 (± 9.2) years. Women with a high coffee consumption were on average younger, less educated, drank less tea, ate more buns, cookies and cakes and more likely to smoke. Other characteristics such as BMI, age at menarche, number of children, oral contraceptive use, post menopausal hormone use, total energy intake and history of diabetes did not vary substantially with respect to coffee consumption.

Table 4.
Rate Ratios and 95% confidence intervals of coffee consumption in relation to endometrial cancer for women in the Swedish Mammography Cohort.

<table>
<thead>
<tr>
<th>Coffee consumption</th>
<th>≤1 cups</th>
<th>2-3 cups</th>
<th>≥4 cups</th>
<th>Per 1 cup *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No of cases</td>
<td>271</td>
<td>312</td>
<td>94</td>
<td></td>
</tr>
<tr>
<td>RR (95% CI) †</td>
<td>1.00 (ref)</td>
<td>0.78 (0.64-0.95)</td>
<td>0.75 (0.58-0.97)</td>
<td>0.90 (0.83-0.97)</td>
</tr>
<tr>
<td>Normal weight (BMI 20-25)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No of cases</td>
<td>77</td>
<td>132</td>
<td>37</td>
<td></td>
</tr>
<tr>
<td>RR (95% CI) ‡</td>
<td>1.00 (ref)</td>
<td>1.21 (0.84-1.73)</td>
<td>1.13 (0.72-1.78)</td>
<td>1.00 (0.88-1.15)</td>
</tr>
<tr>
<td>Overweight (BMI 26-30)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No of cases</td>
<td>94</td>
<td>94</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td>RR (95% CI) ‡</td>
<td>1.00 (ref)</td>
<td>0.65 (0.46-0.92)</td>
<td>0.72 (0.46-1.14)</td>
<td>0.88 (0.77-1.00)</td>
</tr>
<tr>
<td>Obese (BMI &gt;30)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No of cases</td>
<td>80</td>
<td>63</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>RR (95% CI) ‡</td>
<td>1.00 (ref)</td>
<td>0.50 (0.34-0.74)</td>
<td>0.54 (0.32-0.93)</td>
<td>0.80 (0.69-0.93)</td>
</tr>
<tr>
<td>Never smokers</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No of cases</td>
<td>121</td>
<td>140</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>RR (95% CI) §</td>
<td>1.00 (ref)</td>
<td>0.83 (0.62-1.12)</td>
<td>0.66 (0.41-1.07)</td>
<td>0.89 (0.79-1.00)</td>
</tr>
<tr>
<td>Long-term coffee consumption</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No of cases</td>
<td>224</td>
<td>304</td>
<td>149</td>
<td></td>
</tr>
<tr>
<td>RR (95% CI) †</td>
<td>1.00 (ref)</td>
<td>0.82 (0.69-0.98)</td>
<td>0.85 (0.69-1.05)</td>
<td>0.93 (0.86-1.00)</td>
</tr>
</tbody>
</table>

* Cup size standardized to 200 gram
† Rate ratios from Cox proportional hazards models adjusted for age in months, BMI (<20, 20-25, 26-30, >30) and smoking (never/ever/missing).
‡ Rate ratios from Cox proportional hazards models adjusted for age in months, BMI (continuously) and smoking (never/ever/missing).
§ Rate ratios from Cox proportional hazards models adjusted for age in months, BMI (<20, 20-25, 26-30, >30).
Overall, coffee consumption was statistically significant and inversely associated with endometrial cancer risk in both analyses adjusted for age and further adjusted for BMI and smoking (Table 4). We also examined whether the observed association differed according to BMI status, by stratifying the cohort into groups with BMI 20-25, 25-30, >30 kg/m². We observed a decreased risk associated with coffee intake among overweight and obese women (Table 4). To eliminate the possible residual confounding by smoking we performed an analysis confined to never smokers only (including 20,348 women and 283 cases; Table 4). We further investigated the association using updated information on coffee consumption from the second questionnaire in the cohort (Table 4).

There was a statistically significant interaction between coffee consumption and BMI, \( p_{\text{interaction}} < 0.001 \). Women drinking 4 or more coffee cups per day and had a normal body weight (BMI 20-25 kg/m²) had a substantially lower risk compared to those who were obese (BMI >30) and drank 1 cup of coffee or less per day (Figure 9).

**Figure 9.**
Rate ratios of coffee consumption stratified by body mass index in relation with endometrial cancer for women in the Swedish Mammography Cohort.

Rate ratios (RR) from Cox proportional hazards models adjusted for age and smoking.

\( p_{\text{interaction}} < 0.001 \)

All P-values from RRs were <0.05.
We evaluated the possible modification by leisure time physical inactivity (sitting/watching TV 5 hours or more per day) and coffee consumption in a subset of the cohort including 32,649 women and 240 cases, we combined the two upper categories of coffee consumption. However, the interaction did not reach statistical significance. Inactive women drinking more than 2 cups of coffee had a RR of 0.58 (95% CI 0.23-1.49) compared to inactive women drinking less than 2 cups of coffee. The corresponding estimate among active women was 1.09 (95% CI 0.82-1.44).

We also evaluated the observed association among diabetic women. The analysis included 2505 diabetic women and 47 endometrial cancer cases; combining the two upper categories of coffee consumption the association was strong among diabetic women. Diabetic women drinking more than 2 cups of coffee had a RR of 0.48 (95% CI 0.22-1.05) compared to diabetic women drinking less than 2 cups of coffee.
Compared to women with a low glycemic load intake, women with a high glycemic load were, on average, older, less likely to have a postsecondary education or to have ever smoked. Other characteristics did not vary appreciably.

Overall using the baseline cohort, there were no associations of carbohydrate intake, glycemic index, or glycemic load with endometrial cancer risk either in age-adjusted analysis or in analysis adjusted for known and potential risk factors for endometrial cancer (Table 5).

Table 5.
Rate ratios and 95% confidence intervals of endometrial cancer according to carbohydrate intake (gram/day), glycemic index, and glycemic load among 61,226 women, 1987-2005

<table>
<thead>
<tr>
<th>Quintile</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbohydrate intake</td>
<td>No. of cases</td>
<td>96</td>
<td>124</td>
<td>112</td>
<td>142</td>
</tr>
<tr>
<td>Rate ratios</td>
<td>1.00</td>
<td>1.19</td>
<td>1.03</td>
<td>1.24</td>
<td>1.12</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(0.90-1.56)</td>
<td>(0.78-1.36)</td>
<td>(0.95-1.61)</td>
<td>(0.85-1.47)</td>
<td></td>
</tr>
<tr>
<td>Glycemic index</td>
<td>No. of cases</td>
<td>110</td>
<td>130</td>
<td>126</td>
<td>119</td>
</tr>
<tr>
<td>Rate ratios</td>
<td>1.00</td>
<td>1.09</td>
<td>1.06</td>
<td>1.01</td>
<td>1.00</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(0.84-1.41)</td>
<td>(0.81-1.37)</td>
<td>(0.78-1.32)</td>
<td>(0.77-1.30)</td>
<td></td>
</tr>
<tr>
<td>Glycemic load</td>
<td>No. of cases</td>
<td>100</td>
<td>123</td>
<td>115</td>
<td>126</td>
</tr>
<tr>
<td>Rate ratios</td>
<td>1.00</td>
<td>1.14</td>
<td>1.03</td>
<td>1.09</td>
<td>1.15</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(0.87-1.50)</td>
<td>(0.78-1.36)</td>
<td>(0.83-1.42)</td>
<td>(0.88-1.51)</td>
<td></td>
</tr>
</tbody>
</table>

*Cox proportional hazards models were used to calculate rate ratios adjusted for age in months. Carbohydrate intake, glycemic index, and glycemic load were adjusted for total energy intake.*

We also performed analysis stratified by BMI; non-significant positive associations of carbohydrate intake and glycemic load with endometrial cancer risk were observed among obese women (BMI ≥30 kg/m²). Among obese women, those in the highest quintile of carbohydrate intake or glycemic load had (statistically non-significant) approximately 70% and 60%, increased risk of endometrial cancer respectively, compared to those in the lowest quintile. Tests for interaction between BMI and carbohydrate intake or glycemic load in relation to risk of endometrial cancer were not statistically significant.

In the sub-sample analysis using exposure data from the second questionnaire and with follow-up from 1998 through June 2005, 214 endometrial cancer cases were available for analysis. We observed no overall association between carbohydrate intake, glycemic index, or glycemic load and endometrial cancer risk; the age-adjusted RRs for the highest compared with the lowest quartile were 1.32 (95% CI 0.88-1.97) for carbohydrate intake, 1.20 (95% CI 0.81-1.78) for glycemic index, and 1.17 (95% CI 0.78-1.75) for glycemic load.
In analyses stratified by physical activity, there were non-significant positive associations between carbohydrate intake and glycemic load with risk of endometrial cancer among inactive women, but not among active women. Tests for interaction between physical activity and carbohydrate intake or glycemic load in relation to endometrial cancer were not statistically significant. Among women who were both physically inactive and overweight (BMI \( \geq 25 \) kg/m\(^2\)), the RRs for the highest versus the lowest quartile were 1.90 (95% CI 0.84-4.31) for carbohydrate intake, 1.73 (95% CI 0.72-4.17) for glycemic index and 2.99 (95% CI 1.17-7.67) for glycemic load (Figure 10).

Figure 10.
Rate ratios of endometrial cancer according to quartiles of carbohydrate intake, glycemic index and glycemic load among physically inactive women with a BMI \( \geq 25 \) kg/m\(^2\) from the SMC.

Cox proportional hazards models were used to calculate rate ratios adjusted for age in months. Carbohydrate intake, glycemic index, and glycemic load were adjusted for total energy intake.

Since glycemic load was the only variable that was associated with endometrial cancer in our previous analyses we choose to rerun the analyses including the new cases diagnosed in the cohort after 2005 (Table 6).

Using the baseline data and stratifying by BMI there was a suggestion of an association between high glycemic load and endometrial cancer risk among overweight and obese women. Using the data from the second questionnaire where more detailed food questions were asked, there was statistically significant evidence for an association between high glycemic load and endometrial cancer among overweight and obese women (Table 6).
Table 6. Rate ratios and 95% confidence intervals of endometrial cancer according to quintiles of glycemic load, stratified by body mass index

<table>
<thead>
<tr>
<th>Quintile of glycemic load</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>(P_{\text{trend}})</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline 1987-2007</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25 kg/m^2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of cases</td>
<td>52</td>
<td>47</td>
<td>57</td>
<td>62</td>
<td>51</td>
<td></td>
</tr>
<tr>
<td>Rate Ratios (95% CI)</td>
<td>1.00</td>
<td>0.88</td>
<td>1.16</td>
<td>1.19</td>
<td>0.98</td>
<td>(0.59-1.32)</td>
</tr>
<tr>
<td>25-&lt;30 kg/m^2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of cases</td>
<td>30</td>
<td>44</td>
<td>49</td>
<td>43</td>
<td>59</td>
<td></td>
</tr>
<tr>
<td>Rate Ratios (95% CI)</td>
<td>1.00</td>
<td>1.42</td>
<td>1.41</td>
<td>1.15</td>
<td>1.49</td>
<td>(0.87-2.32)</td>
</tr>
<tr>
<td>≥30 kg/m^2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of cases</td>
<td>24</td>
<td>36</td>
<td>22</td>
<td>38</td>
<td>46</td>
<td></td>
</tr>
<tr>
<td>Rate Ratios (95% CI)</td>
<td>1.00</td>
<td>1.24</td>
<td>0.80</td>
<td>1.28</td>
<td>1.75</td>
<td>(0.68-2.26)</td>
</tr>
<tr>
<td><strong>SMC 1997-2007</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25 kg/m^2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of cases</td>
<td>18</td>
<td>25</td>
<td>16</td>
<td>23</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>Rate Ratios (95% CI)</td>
<td>1.00</td>
<td>1.30</td>
<td>0.84</td>
<td>1.15</td>
<td>1.29</td>
<td>(0.71-2.41)</td>
</tr>
<tr>
<td>25-&lt;30 kg/m^2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of cases</td>
<td>7</td>
<td>18</td>
<td>20</td>
<td>23</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Rate Ratios (95% CI)</td>
<td>1.00</td>
<td>2.50</td>
<td>2.56</td>
<td>2.67</td>
<td>2.48</td>
<td>(1.03-6.03)</td>
</tr>
<tr>
<td>≥30 kg/m^2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of cases</td>
<td>7</td>
<td>15</td>
<td>16</td>
<td>20</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Rate Ratios (95% CI)</td>
<td>1.00</td>
<td>2.27</td>
<td>2.35</td>
<td>2.96</td>
<td>1.79</td>
<td>(0.90-5.72)</td>
</tr>
</tbody>
</table>

* Cox proportional hazards models were used to calculate rate ratios adjusted for age in months. Glycemic load was adjusted for total energy intake using the residual method. The number of cases may not add up to the total number of cases because of missing data on body mass index.
ALCOHOL - PAPER III

Women with high alcohol consumption were younger, had a lower BMI, more among them used oral contraceptives and postmenopausal hormones, were more educated, had less diabetes and tended to smoke more. Other characteristics such as age at menarche, number of children, age at menopause and total energy intake did not vary substantially with respect to alcohol consumption.

Alcohol drinking at baseline was overall not associated with endometrial cancer risk (Table 7).

Table 7.
Rate Ratios and 95% confidence intervals of alcohol consumption in relation to endometrial cancer for 61 226 women in the Swedish Mammography Cohort.

<table>
<thead>
<tr>
<th>Alcohol consumption (gram/day)</th>
<th>Non-drinkers</th>
<th>&lt;3.4</th>
<th>3.4-9.9</th>
<th>≥10.0</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No of cases</td>
<td>268</td>
<td>273</td>
<td>122</td>
<td>24</td>
</tr>
<tr>
<td>Age-adjusted RR</td>
<td>1.00</td>
<td>0.91</td>
<td>0.77</td>
<td>0.87</td>
</tr>
<tr>
<td>(95% CI)*</td>
<td>(0.77-1.08)</td>
<td>(0.61-0.96)</td>
<td>(0.57-1.34)</td>
<td></td>
</tr>
<tr>
<td>Multivariable adjusted RR</td>
<td>1.00</td>
<td>1.01</td>
<td>0.95</td>
<td>1.12</td>
</tr>
<tr>
<td>(95% CI)†</td>
<td>(0.85-1.20)</td>
<td>(0.75-1.19)</td>
<td>(0.73-1.71)</td>
<td></td>
</tr>
</tbody>
</table>

* Rate ratios from Cox proportional hazards models adjusted for age in months.
† Rate ratios from Cox proportional hazards models adjusted for age in months, BMI (<20, 20-25, 26-30, >30) and smoking (never/ever/missing).

Long term alcohol consumption, treating alcohol as a cumulative average of the alcohol intake at the two measurements, was not associated with endometrial cancer, RRs for the three upper categories of alcohol consumption as compared to the lowest one were; 1.01 (95% CI 0.84-1.22); 1.01 (95% CI 0.80-1.27) and 1.09 (95% CI 0.71-1.67), respectively. We also performed sub-sample analysis on never smokers since smoking has been shown to decrease the risk of endometrial cancer and also be correlated with higher alcohol consumption. In this sample including 20 516 women and 287 cases, RRs for the three upper categories of alcohol consumption as compared to the lowest one were: 0.93 (95% CI 0.71-1.22); 0.96 (95% CI 0.68-1.37) and 0.78 (95% CI 0.31-1.94), respectively.

To explore possible sources of effect modification we also performed stratifications by age, BMI, folic acid intake or postmenopausal hormone use. Results from these analyses did not differ between different strata.
META-ANALYSIS: ALCOHOL - PAPER IV

There were 7 independent cohort studies that met the inclusion criteria (Table 2). Three studies were conducted in North America\textsuperscript{105, 135, 143} and 4 in Europe\textsuperscript{68, 134, 169, 170}. All 7 cohort studies, including 1,478,663 participants and 5,881 endometrial cancer cases, reported dose-response data on alcohol and endometrial cancer risk, and a wide range of alcohol intakes.

Highest versus lowest category

The comparison of the highest versus lowest category of alcohol intake (Figure 11) showed an increase of endometrial cancer with higher intake of alcohol albeit not statistically significant (summary RR 1.17; 95% CI 0.95-1.44). We found no evidence of heterogeneity across studies or evidence for publication bias concerning alcohol and risk of endometrial cancer incidence. The \(P\)-value for Egger’s regression asymmetry test was 0.21.

**Figure 11.**

Summary of relative risk estimates (highest vs. lowest category) of endometrial cancer risk associated with alcohol consumption in cohort studies

<table>
<thead>
<tr>
<th>Author, year</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allen, 2009</td>
<td>1.00 (0.86, 1.17)</td>
</tr>
<tr>
<td>Friberg, 2009</td>
<td>1.09 (0.71, 1.68)</td>
</tr>
<tr>
<td>Setliawan, 2008</td>
<td>2.01 (1.30, 3.11)</td>
</tr>
<tr>
<td>Loerbroks, 2007</td>
<td>1.78 (0.88, 3.60)</td>
</tr>
<tr>
<td>Jain, 2000</td>
<td>1.00 (0.67, 1.50)</td>
</tr>
<tr>
<td>Terry, 1999</td>
<td>1.10 (0.50, 2.41)</td>
</tr>
<tr>
<td>Gapstur, 1993</td>
<td>1.01 (0.67, 1.53)</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td>1.17 (0.95, 1.44)</td>
</tr>
</tbody>
</table>

Squares represent study-specific relative risks (RRs) and the sizes of the squares reflect the statistical weight (inverse of the variance) that each study contributed to the summary estimate, horizontal lines represent 95% confidence intervals (CIs), the diamond represents the summary estimate and its 95% CI. Test for heterogeneity \(Q= 10.94; P = 0.091; I^2=45\%\).
Smoking and body mass index are potentially the most important known confounders of an inverse or positive association between alcohol and endometrial cancer risk, respectively. When we restricted the meta-analysis to studies that controlled for these variables the summary RR was slightly higher but remained not significant (summary RR 1.29; 95% CI 0.90-1.86).

**Dose-response**

We next performed a dose-response meta-analysis to be able to take into account the differences in the range of alcohol intake assessed by the studies. We modeled the relationship between endometrial cancer risk and alcohol consumption using restricted cubic splines. We found some evidence of non-linear association (P for linearity = 0.001) between alcohol intake and endometrial cancer risk. For exposures lower than one drink (1 drink = 13 grams of ethanol) per day there was an inverse association with endometrial cancer risk. Compared to non-drinkers, the summary endometrial cancer risk was lower by 6% (95% CI 0.90-0.98) for consumption up to 0.5 drinks per day and by 10% (95% CI 0.83-0.98) for 0.5 drinks per day and up to 1 drink (Figure 12).

The risk of endometrial cancer appeared increased after two drinks of alcohol per day. Compared to non-drinkers, the summary endometrial cancer risk was higher by 6% (95% CI 0.93-1.20) for 1.5 and up to 2 drinks per day, by 16% (95% CI 0.98-1.38) for 2 and up to 2.5 drinks per day and by 27% (95% CI 1.02-1.60) for 2.5 drinks per day or more (Figure 12).

**Figure 12.**

Dose-response relationship between alcohol consumption (drink/day) and endometrial cancer risk, estimated with a random-effect meta-regression restricted cubic spline model.

The grey shaded area represents the 95% confidence limits for the fitted curve. Test for heterogeneity $Q=21.98; P$-heterogeneity $=0.34; I^2=9\%$. 

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Meta-analysis including case-control studies
We also performed a meta-analysis including case-control studies (Table 3) with available risk estimates and at least controlling for age (results not included in paper IV). The summary RR for the highest category of alcohol compared to the lowest one showed a non-significant decrease in risk for endometrial cancer among case-control studies, in contrast to the increased risk observed among cohort studies (Table 8). The association was somewhat stronger among hospital-based case-control studies compared to population-based ones. Studies performed in Europe showed an increase in risk whereas North American and Asian studies showed a decrease in risk. However, the studies were very heterogeneous and only part of them reported dose-response data therefore we chose not to include them in paper IV.

Table 8.
Summary relative risk estimates and 95% confidence intervals for cohort and case-control studies of the association between alcohol and endometrial cancer incidence by study design and geographical area

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of studies</th>
<th>Summary RR (95% CI)</th>
<th>Q</th>
<th>Between studies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>P</td>
</tr>
<tr>
<td><strong>Study design</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cohort</td>
<td>7</td>
<td>1.17 (0.95-1.44)</td>
<td>10.94</td>
<td>0.09</td>
</tr>
<tr>
<td>Case-control†</td>
<td>11</td>
<td>0.90 (0.71-1.13)</td>
<td>23.23</td>
<td>0.01</td>
</tr>
<tr>
<td>Population-based</td>
<td>6</td>
<td>0.89 (0.72-1.09)</td>
<td>6.87</td>
<td>0.23</td>
</tr>
<tr>
<td>Hospital-based</td>
<td>5</td>
<td>0.80 (0.46-1.41)</td>
<td>13.77</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>Continent‡</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Europe</td>
<td>7</td>
<td>1.10 (0.90-1.35)</td>
<td>12.58</td>
<td>0.05</td>
</tr>
<tr>
<td>North America</td>
<td>8</td>
<td>0.97 (0.74-1.27)</td>
<td>19.59</td>
<td>0.01</td>
</tr>
<tr>
<td>Asia</td>
<td>3</td>
<td>0.79 (0.43-1.47)</td>
<td>2.37</td>
<td>0.30</td>
</tr>
</tbody>
</table>

* Test for heterogeneity between case-control and cohort studies. 0.005  
† Test for heterogeneity between population-based and hospital-based case-control studies 0.06  
‡ Test for heterogeneity between continents 0.005
META-ANALYSIS: DIABETES - PAPER V

Study Characteristics

25 independent studies met the predefined inclusion criteria. Of these 25 studies, five were cohort studies that used incidence and/or mortality rate ratios as the measure of relative risk \(^{68, 171-174}\) (Table 1, paper V), and 13 were case-control studies that used odds ratios as the measure of risk \(^{12, 17, 74, 175-184}\) (Table 2, paper V), seven were cohort studies that used standardized incidence and or /mortality ratio as the measure of relative risk \(^{185-191}\) (Table 3, paper V).

In the primary meta-analysis of diabetes and endometrial cancer incidence, we included three cohort studies that reported incidence rate ratios \(^{68, 171, 174}\) and 13 case-control studies \(^{12, 17, 74, 175-184}\). These 16 studies included a total of 96,003 participants. The 4 cohort studies \(^{185, 187-189}\) that reported standardized incidence ratios were analyzed separately.

For the meta-analysis of diabetes and endometrial cancer mortality, we included the two cohort studies that reported mortality rate ratios \(^{172, 173}\). These two studies enrolled a total of 896 participants. The 4 cohort studies \(^{185, 187-189}\) that reported standardized incidence ratios and the 3 cohort studies \(^{185, 190, 191}\) that reported standardized mortality ratios were analyzed separately.

Three studies reported on type 1 diabetes and incidence of endometrial cancer, one case control study \(^{175}\) and two studies providing standardized incidence ratios \(^{185, 186}\). One study reported on type 1 diabetes and endometrial cancer mortality providing a standardized mortality ratio including only one case of endometrial cancer \(^{185}\).

Endometrial Cancer Incidence

Individual study results and the overall summary result for 3 cohort and 13 case-control studies of diabetes and endometrial cancer incident are shown in Figure 13. Twelve of these 16 studies found a statistically significant positive association between diabetes and endometrial cancer incidence (range of individual RRs 1.30 to 7.75; summary RR for all 16 studies 2.10, 95% CI 1.75-2.53).
**Figure 13.**
Association between diabetes and endometrial cancer incidence in cohort and case-control studies.

**Test for heterogeneity among cohort studies:** $Q=1.01; P=0.60; I^2=0.0\%$

**Test for heterogeneity among case-control studies:** $Q=28.34; P=0.01; I^2=57.7\%$

**Test for heterogeneity between sub-groups:** $Q=2.70; P=0.10$

Studies are ordered by publication year and stratified on design. Squares=study specific RR estimate (size of the square reflects the study-specific statistical weight, i.e. the inverse variance); horizontal lines=95% CI; diamond=summary relative risk estimate and its corresponding 95% CI.

We then conducted subgroup meta-analyses by study design, geographical area, control group (for case-control studies) and adjustments (full versus only adjusted for age) (Table 9). The association between diabetes and endometrial cancer incidence was somewhat stronger in Europe than in USA, and among case control studies. When taking adjustments into consideration the studies adjusting only for age reported a stronger association than the studies adjusting the relative risk with a full model, indicating a presence of confounding.
Table 9.
Summary relative risk estimates and 95% confidence intervals for case-control and cohort studies of the association between diabetes and endometrial cancer incidence by study design, geographical area and adjustments.

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of studies</th>
<th>Summary RR (95% CI)</th>
<th>Q</th>
<th>(P_{\text{heterogeneity}})</th>
<th>(I^2\text{statistics, %})</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study design</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cohort studies</td>
<td>3</td>
<td>1.62 (1.21-2.16)</td>
<td>1.01</td>
<td>0.60</td>
<td>0.0</td>
</tr>
<tr>
<td>Case-Control *</td>
<td>13</td>
<td>2.22 (1.80-2.74)</td>
<td>28.34</td>
<td>0.01</td>
<td>57.7</td>
</tr>
<tr>
<td>Population based †</td>
<td>7</td>
<td>2.04 (1.58-2.63)</td>
<td>13.60</td>
<td>0.03</td>
<td>55.9</td>
</tr>
<tr>
<td>Hospital based</td>
<td>6</td>
<td>2.51 (1.78-3.56)</td>
<td>10.11</td>
<td>0.07</td>
<td>50.5</td>
</tr>
<tr>
<td><strong>Geographical area ‡</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>United States</td>
<td>8</td>
<td>1.70 (1.47-1.98)</td>
<td>5.19</td>
<td>0.64</td>
<td>0.0</td>
</tr>
<tr>
<td>Europe</td>
<td>6</td>
<td>2.51 (1.83-3.45)</td>
<td>12.16</td>
<td>0.03</td>
<td>59.0</td>
</tr>
<tr>
<td>Other</td>
<td>2</td>
<td>4.10 (2.09-8.01)</td>
<td>0.70</td>
<td>0.40</td>
<td>0.0</td>
</tr>
<tr>
<td><strong>Adjustments §</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full</td>
<td>11</td>
<td>1.92 (1.58-2.33)</td>
<td>20.12</td>
<td>0.03</td>
<td>50.3</td>
</tr>
<tr>
<td>Age</td>
<td>5</td>
<td>2.74 (1.87-4.00)</td>
<td>6.83</td>
<td>0.15</td>
<td>41.5</td>
</tr>
</tbody>
</table>

All statistical tests were two-sided.

* Test for heterogeneity between case-control and cohort studies 0.10
† Test for heterogeneity between population-based and hospital-based case-control studies 0.03
‡ Test for heterogeneity between geographical areas 0.00
§ Test for heterogeneity between studies adjusting only for age or using a full model 0.02

A positive association was observed between diabetes and endometrial cancer incidence in the cohort studies that reported standardized incidence ratios \(^{185, 187-189}\) (summary RR 1.63 95% CI 1.30-2.05; test for heterogeneity Q=9.60; \(p = 0.02; I^2 = 68.8\%\)).

There was no evidence for publication bias concerning diabetes and risk of endometrial cancer incidence when we constructed a funnel plot. The P-value for Egger’s regression asymmetry test was 0.14 (i.e. a low probability for publication bias).
Endometrial Cancer Mortality
Of the two cohort studies of diabetes and mortality from endometrial cancer\textsuperscript{172, 173}, one\textsuperscript{172} reported a statistically significant positive association, while the other\textsuperscript{173} observed a non-statistically significant positive association. When both studies were analyzed, a positive, but non-significant association between diabetes and mortality from endometrial cancer was found (summary RR = 1.58 95% CI 0.94-2.66; test for heterogeneity $Q = 1.63$; $p = 0.20$; $I^2 = 38.7\%$). No association was observed between diabetes and endometrial cancer mortality in the three cohort studies that reported standardized mortality ratios\textsuperscript{185, 190, 191} (summary RR 0.97 95% CI 0.52-1.81; test for heterogeneity $Q = 4.76$; $p = 0.09$; $I^2 = 58.0\%$).

Type 1 diabetes
One case-control study and two cohorts reporting standardized incidence ratios reported on the association between type 1 diabetes and endometrial cancer incidence\textsuperscript{175, 185, 186}. When the three studies were analyzed, a statistically significant positive association between type 1 diabetes and incidence of endometrial cancer was found (summary RR 3.15 95% CI 1.07-9.29; test for heterogeneity $Q = 6.66$; $p = 0.04$; $I^2 = 70.0\%$).
DISCUSSION

MAIN FINDINGS

Coffee - Paper I
Our study assessed the effect of caffeinated coffee since decaffeinated coffee was virtually non-existent in Sweden during the time-period. Daily coffee consumption was associated with lower risk for endometrial cancer. Women drinking 2 cups of coffee or more a day had a statistically significantly decreased risk of endometrial cancer. Each additional cup of coffee (1 cup = 200g) was associated with 10% reduced risk of endometrial cancer among all women. Risk reduction was largely confined to overweight and obese women who are at increased risk for endometrial cancer. Among these women, each additional cup of coffee consumed daily decreased the risk of endometrial cancer by 12% and 20%, respectively.

The association between coffee consumption and endometrial cancer risk has only been previously studied twice in the context of a prospective cohort study. Eight previous case-control studies have investigated a possible association. Our results confirm and extend data from the previous cohort studies and the previous case-control studies, showing a decreased risk of endometrial cancer in relation to high coffee consumption, but are not in agreement with the two studies that showed a non-significant positive association.

Carbohydrates, glycemic index and glycemic load - Paper II
We found no overall associations between carbohydrate intake, glycemic index, or glycemic load and the incidence of endometrial cancer. However, among overweight women with low physical activity, we observed a non-significant 1.9-fold increase in risk of endometrial cancer for those who had a high carbohydrate intake and a statistically significant 3-fold increase for those who had a high glycemic load.

Our findings are broadly consistent with those from the Iowa Women’s Health Study and the Canadian National Breast Screening Study. The Iowa Women’s Health Study (415 cases), showed no association of glycemic index or glycemic load with endometrial cancer risk in the whole cohort, but found a statistically significant 1.9-fold increase in endometrial cancer risk for the highest versus lowest quintile of glycemic load among obese non-diabetic women. Similarly, the Canadian National Breast Screening Study (426 cases) found a statistically significant 1.9-fold increased risk of endometrial cancer comparing the highest with the lowest quartile of glycemic load among obese women. In agreement with our finding, the Canadian National Breast Screening Study also observed an elevated risk of endometrial cancer associated with a high glycemic load among physically inactive women, although this association was not significant (highest versus lowest quartile: RR 1.50 95% CI 0.93-2.42). In a hospital-based case-control study conducted in Italy and Switzerland (with 410 cases), there was a suggestion of a stronger positive relation between glycemic index and risk of endometrial cancer in overweight women (highest versus lowest quintile: odds ratio 2.28 95% CI 1.27-4.12) than in lean women (highest versus lowest quintile: odds ratio 1.62 95% CI 1.86-3.05).
**Alcohol - Paper III**
We found no relation between alcohol consumption and endometrial cancer risk. Our results are in agreement with previous studies, showing no association between alcohol consumption and endometrial cancer risk \(^\text{10, 45, 97, 98, 105, 134, 135, 137-142}\), but not with studies showing either an increase or decrease in risk in relation to endometrial cancer \(^\text{68, 99, 136, 143-145}\). We have in our study relatively low levels of alcohol intake and the null-results for consumption of up to 1 drink per day are in agreement with clinical studies showing an increase in estrogen levels with alcohol consumption in the magnitude of 2 drinks per day \(^\text{192}\).

**Meta-analysis: Alcohol - Paper IV**
In this meta-analysis, women drinking moderate amounts of alcohol had a lower risk for endometrial cancer. Compared to non-drinkers, the summary endometrial cancer risk was lower by 6% (95% CI 0.90-0.98) for consumption up to 0.5 drinks per day and by 10% (95% CI 0.83-0.98) for intake of 0.5 to 1 drinks. We found some evidence for an increased risk for endometrial cancer for an alcohol intake higher than two alcohol drinks per day; compared to non-drinkers, the summary risk was higher by 16% (95% CI 0.98-1.38) for 2 to 2.5 drinks per day and by 27% (95% CI 1.02-1.60) for more than 2.5 drinks per day.

We chose not to include analysis from case-control studies in the paper; the case-control studies showed using the highest versus lowest approach an overall summary RR of 0.90 (95% CI 0.71-1.13) in contrast to the summary RR from prospective cohort studies 1.17 (95% CI 0.95-1.44).

**Meta-analysis: Diabetes - Paper V**
Findings from this meta-analysis show that individuals with diabetes have an approximately 2.1 times increased risk of developing endometrial cancer compared with non-diabetic individuals. We also found that individuals with type 1 diabetes had a three-fold increased risk for endometrial cancer incidence. However, this meta-analysis does not support that diabetes is associated with increased risk of endometrial cancer mortality. All previous studies have consistently shown a positive association between diabetes and endometrial cancer incidence; however heterogeneity does exist. Examination of the heterogeneity suggests that the differences were due to the reported strength of the effect estimate. When stratifying on study design the heterogeneity between subgroups were p=0.10. The summary relative risk was consistent but slightly higher for case-control than cohort studies, and among studies conducted in Europe versus studies carried out in United States. The studies that only adjusted for age also showed a slightly stronger effect estimate, probably due to lack of controlling for important confounders such as BMI. Diabetes and endometrial cancer findings were also consistent in cohorts reporting standardized incidence ratios.
METHODOLOGICAL CONSIDERATIONS

There are several potential sources of bias in observational epidemiological studies on diet. There are difficulties in measuring food intakes, correlation between intakes of different foods, nutrient content, recall and selection biases and confounding. Measurement errors inevitably occur when assessing diet by a questionnaire. The possible misclassification that can be the result may attenuate risk estimates and reduce the statistical power to detect a true relationship. Correlations among food make it difficult to examine independent effects of a specific food on a risk of a disease. The various biases that might influence our results are discussed below.

This thesis includes two types of studies. The risk of endometrial cancer in relation to coffee, carbohydrates and alcohol (paper I-III) was investigated in a population-based prospective cohort study. The risk of endometrial cancer in relation to alcohol and diabetes was explored using meta-analysis (paper IV and V).

**Precision – absence of random errors**

Precision is defined as absence of random errors. It is estimated by 95% confidence intervals and depends largely on sample size, prevalence of the exposure and on the degree of exposure misclassification. The large sample size in the Swedish Mammography Cohort improves the precision of the risk estimates, as does the very large sample size in the meta-analyses, which also gives us an opportunity to examine consistency.

**Validity – absence of systematic errors**

**Selection bias**

In general, selection bias can arise in studies in three situations: 1) if the relation between the exposure and outcome is different for those who participate versus those who should theoretically be eligible for the study, 2) if there are systematic differences in characteristics between those who are selected versus those who are not, 3) if there are differences in loss to follow-up among exposed versus unexposed subjects.

The prospective nature of our cohort analysis fulfills the time sequence criterion for causality and makes it highly unlikely that the associations we observed were due to selection biases. Selection bias tends to be a minor problem in cohort studies due to internal comparisons. In prospective studies, since exposure is assessed prior to the occurrence of disease, it is unlikely that the outcomes would influence the classification of exposure.

Non-identification of cases may occur if an individual is lost to follow-up and may introduce a systematic error in cohort studies. Complete case identification is therefore important. In the Swedish Mammography Cohort, endometrial cancer was ascertained using the National Swedish Cancer Registry and the Regional Cancer Registry, hence the follow-up is close to 100%. Thus, our results should not be biased due to incomplete follow-up of our cohort.
Publication bias
Publication bias might be a problem in meta-analyses. The bias is caused by the tendency of researchers to write and submit, and reviewers and editors to accept and publish results depending on the magnitude and direction of the association. For example, studies observing statistically significant results are more likely to be published. Therefore, studies showing an association are more likely to be included in a meta-analysis than “negative” studies that show no association; thus potentially introduce bias.

In our meta-analyses on alcohol, diabetes and endometrial cancer, formal statistical tests and inspections of funnel plots did not provide evidence for publication bias. However, because of the small number of studies included especially in the alcohol and endometrial cancer meta-analysis, we had limited statistical power to detect any publication bias. The presence of possible publication bias could have resulted in an overestimation of the summary relative risks.

Information bias
There are two types of information biases that might occur in an epidemiological study: systematic measurement- and random errors. Systematic measurement errors, also referred to as differential misclassification, may affect the estimate in any direction. Random errors, also known as non-differential misclassification, usually dilute any observed risk estimate towards the null.

Misclassification of the exposure in the cohort study cannot be ruled out. Since exposure was assessed twice ten years apart, changes in exposures during the follow-up are possible. Due to the prospective nature of the studies, any misclassification is most likely to be non-differential thus leading to attenuation of our risk estimates. The use of cumulatively updated dietary data reduces random within-person measurements error. Misclassification of the outcome in the cohort is expected to have been minimal. Identification of endometrial adenocarcinoma cases was made by linkage with the national and regional Swedish cancer registries. The proportion of morphologically confirmed cases in the registries is 99%.

Our meta-analyses on alcohol and diabetes must be interpreted in the context of limitations of the available data. Some misclassification of alcohol is probable. However, since we only include prospective studies in our meta-analysis on alcohol and endometrial cancer, such non-differential misclassification would be expected to influence the results toward the null. However, we cannot rule out the possibility that part of the lowered relative risk observed among women drinking up to 1 drink per day, is because the reference category may include former drinkers and women with health problems, these women might be at a higher risk for developing endometrial cancer. Many studies on diabetes and endometrial cancer did not distinguish between type 1 and type 2 diabetes. On the basis of relative prevalence of these two types in Europe and USA, the vast majority of cases are type 2 diabetes. Since diabetes is an under-diagnosed disease, some degree of misclassification of exposure of diabetes is probable, but such non-differential misclassification would be expected to attenuate the true relationship between diabetes and endometrial cancer incidence.
Recall bias is a type of differential misclassification that can occur in case-control studies when cases and controls are requested to recall their diet. It is likely that individuals diagnosed with cancer recall their diet differently than the healthy controls. Cancer cases may also have changed their diet as a result of the disease. Recall bias in case-control studies might be one of the explanations to the different summary RR between alcohol and endometrial cancer risk observed among case-control studies compared to the summary RR observed among cohort studies. Another part of the explanation might be that hospital controls with orthopedic traumas may on average drink more alcohol.

**Confounding**
Confounding is the effect of additional factors that might be responsible for the observed association. Confounders must be associated with both the exposure, and independently of that exposure, be a risk factor for the outcome.

In order to control for confounding in analysis of associations between diet and endometrial cancer (Paper I-III), we adjusted for several established and potential risk factors known to affect the risk of endometrial cancer. Smoking is an important potential confounder when examining relationships between coffee and alcohol and endometrial cancer risk since smoking often is correlated with both coffee and alcohol intake (smokers tend to drink more coffee and alcohol than non-smokers) as well as the outcome - endometrial cancer. In the cohort, smoking was only assessed in the follow-up questionnaire in 1997. This is a major limitation; however, we re-ran the analysis on never-smokers only and found very similar results.

The exposures could also be related to some other unknown risk factor for endometrial cancer that was not controlled for in these studies. Thus, neither confounding nor residual confounding can be completely ruled out, and therefore could hypothetically influence our ability to detect an association.

**Effect modification**
An effect modifier changes (e.g. enhances or diminishes) the effect of the exposure on the outcome and represents an interaction. We observed interaction between coffee intake and BMI as well as between glycemic load, BMI and physical inactivity. The effect of the exposures was more pronounced in the subgroups already at higher risk of insulin resistance and endometrial cancer.

**Generalizability**
Participants of the Swedish Mammography Cohort are from the general population. Hence, our results are most directly generalizable to middle-aged and older Swedish women. Our study population is primarily Caucasian and our findings may not apply directly to other ethnic groups with potentially different genetic susceptibility. However, results on endometrial cancer risk in our cohort study were broadly consistent with previously published studies.
**Statistical power**
The statistical power (precision) of a study depends mostly on the sample size (in a prospective study particularly on the number of cases), the magnitude of the association, exposure prevalence, and the degree of exposure misclassification. Despite the relatively large sample size and the relatively long follow-up of the cohort, the number of endometrial cancer cases was somewhat limited, especially in stratified analysis and in different subgroup analyses.

In our meta-analysis findings on endometrial cancer risk in relation to alcohol the data available was limited. Only three studies were able to evaluate the effect of an alcohol intake above 1.5 drinks per day. More studies would possibly have given a more precise estimate of the risk of endometrial cancer associated with alcohol intake. We could not detect any inverse association between low alcohol intake and endometrial cancer risk in our study population. As demonstrated in the meta-analysis a very large sample size was needed.

Our meta-analysis findings on endometrial cancer mortality in relation to diabetes, and our data on the risk of endometrial cancer incidence in type 1 diabetes, are limited by uncertainty due to a limited number of studies and studies including small numbers of cases.
GENERAL DISCUSSION
Most likely, several mechanisms are involved in the development of endometrial cancer in women. High levels of insulin are a marker of diabetes, obesity and physical inactivity. Insulin has been shown to stimulate the growth of endometrial stromal cells, as well as many other cells in the human body by binding to insulin receptors\textsuperscript{194}.

Coffee has been shown to affect the absorption and metabolism of glucose\textsuperscript{195-197} and may also protect against type 2 diabetes\textsuperscript{125}. Coffee has been shown to improve insulin sensitivity\textsuperscript{124, 198} and has also been inversely related to C-peptide levels\textsuperscript{199}. Coffee also contains phytoestrogens\textsuperscript{200} which have been suggested to decrease the risk of endometrial cancer\textsuperscript{201, 202}. In the Swedish Mammography Cohort coffee was generally the main contributor of caffeine; the correlation coefficient between coffee and caffeine was 0.9. High caffeine intake has been linked to decreased free estrogen levels through higher concentration of circulating SHBG\textsuperscript{203, 204}. Caffeine has, in contrast to coffee, been shown to cause insulin insensitivity\textsuperscript{205}. If the effect of coffee stems from other dietary components of coffee or is an effect of habituation remains to be elucidated.

Figure 14.
Potential mechanisms regarding coffee intake and endometrial cell proliferation
There is an insulin response to intake of carbohydrates, and the response is affected by the quantity and quality of the carbohydrates. A study examining the effect of glycemic index on insulin response reported a 70% reduced insulin response after consumption of a low glycemic index food compared with a high glycemic index food\textsuperscript{206}. There are some studies that suggest that slowly absorbed carbohydrates i.e. low glycemic index foods improve insulin sensitivity through their maintenance of low plasma levels of fatty acids\textsuperscript{113, 207, 208}. The concepts of glycemic index and load are limited to single foods and the ability to predict the response from a whole meal is questionable. Blood glucose and insulin concentrations can also be influenced by other components such as proteins and fats\textsuperscript{209}.

\textbf{Figure 15.}
Potential mechanisms regarding carbohydrate intake and endometrial cell proliferation
There are several mechanisms through which alcohol might influence the risk of endometrial cancer. Moderate alcohol intake (30g of alcohol/day) has been shown to improve insulin sensitivity and reduce fasting insulin concentrations and could thus potentially decrease the risk of endometrial cancer. Higher amounts of alcohol do not seem to have these effects but have been shown to increase levels of estrogen. The postulated mechanisms behind the increase of estrogen include 1. alcohol leads to decreased catabolism of sex steroids in the liver, 2. alcohol can affect aromatase activity which converts androgens to estrogens, and 3. alcohol may also have an effect on the adrenal glands and increase the production of precursors of androgens.

The European Prospective Investigation into Cancer and Nutrition study (EPIC) which is the largest published study on alcohol consumption and sex-steroid concentrations, observed a statistical significant elevation in blood estrogen levels among women that consumed on average approximately 2 or more drinks/day compared to women not consuming alcohol.

**Figure 16.**
Potential mechanisms regarding high and low alcohol intake and endometrial cell proliferation.
Hyperinsulinemia may increase levels of unbound estrogens through decreasing concentrations of circulating SHBG \(^{50, 51}\). Estrogens have been shown to increase endometrial cancer risk by stimulating proliferation of endometrial cells \(^6\), when unopposed by progesterone (especially in postmenopausal women) \(^7, 217\). High prediagnostic C-peptide concentrations, which are an indication of hyperinsulinemia, and a common feature of diabetes have been associated with an elevated risk of endometrial cancer in epidemiologic studies \(^{218}\). Long-term insulin therapy of patients with type 1 diabetes may be an explanation for the increased risk of endometrial cancer incidence found among diabetic women with type 1 diabetes \(^{186}\). Hyperinsulinemia by decreasing levels of IGFBP-1 and IGFBP-3 increases circulating free IGF-1. IGF-1 can bind to and activate IGF-1 receptors in the endometrium thus stimulating cell proliferation \(^{52-56}\). Furthermore, decreased circulating levels of IGFBP-3 may also have a direct regulatory role in cell growth control and cancer \(^{219, 220}\).

Adiponectin is an endogenous insulin sensitizer which lies upstream of all the aforementioned hormonal factors and regulates their circulatory levels \(^36\). Low adiponectin levels are not only associated with higher levels of circulating estradiol and hyperinsulinemia/insulin resistance \(^{61}\), but may also directly alter cell proliferation/apoptosis and angiogenesis \(^{221}\). Low levels of adiponectin have been shown to predict not only diabetes \(^{222}\) but also endometrial cancer incidence \(^{62-65}\) and can thus be a link between diabetes, hormonal abnormalities and endometrial cancer risk. It has been observed that lower circulating levels of adiponectin are closely associated with obesity \(^{57}\). It has also been shown that coffee consumption as well as moderate alcohol intake is related to plasma levels of adiponectin \(^{223, 224}\).

Finally, coffee and wine contain antioxidants that may reduce oxidative stress, an important factor for cancer development \(^{225, 226}\).

In our study, the strongest effect of coffee was observed among overweight and obese women who are at the highest risk for endometrial cancer; this indicates a possible involvement of hypoadiponectinemia, insulin resistance and hyperinsulinemia in the process \(^{34-36, 227}\). Individuals who were both overweight and inactive and had a high glycemic load also had an elevated risk of endometrial cancer. This is consistent with the notion that overweight or inactive women have a greater insulin response to their diet as a result of their physiology compared to lean and active women.

The J-shaped association detected between alcohol and endometrial cancer is in agreement with the theory that a moderate alcohol intake has beneficial effects on insulin levels and sensitivity and could thus potentially lower the risk of endometrial cancer. The J-shaped association also agrees with the notion that at higher intakes of alcohol the effect on estrogen levels would increase the risk of endometrial cancer.

The higher risk for endometrial cancer observed among diabetic women could be due to their reduced adiponectin levels as well as increased insulin and IGF-1 levels. Less amount of adipose tissue has been associated with higher adiponectin levels and lesser degrees of insulin resistance/hyperinsulinemia \(^{36}\).
Public health importance
The evidence for excessive body fatness as a cause for endometrial cancer is convincing. Given the epidemic proportions of obesity in westernized countries and the increasing prevalence of obesity in developing countries, factors that may reduce the risk for the increasingly common cancer in the endometrium is of outmost importance.

Our results suggest that coffee drinking may protect against endometrial cancer, especially among overweight and obese women. Low glycemic load was also associated with a decreased risk for endometrial cancer among overweight and obese women. Both these dietary factors represent lifestyle factors that might be easier to change than body weight.

Our studies on alcohol drinking and endometrial cancer convey the message that a moderate intake of alcohol (up to 1 drink/day) is probably safe. This is in line with recent recommendations on general cancer prevention presented in the recent WCRF/AICR report from 2007. However, larger intakes may increase the risk, not only for endometrial cancer but also for many other common diseases including breast cancer. In context of the large number of women consuming alcohol, this is an important message to put across to women.

Our study on diabetes shows that diabetic women have twice the risk of developing endometrial cancer compared with women without diabetes. This is thus a patient group that is especially important to reach with endometrial cancer protective advices.
CONCLUSIONS

- Coffee consumption was associated with an overall decrease in endometrial cancer risk by on average 10% per cup in the whole study population of women. Among overweight and obese women the respective risk reduction was 12% and 20% for every cup of coffee.

- Intake of carbohydrates, glycemic index and glycemic load was not associated with endometrial cancer risk in the whole study population of women. However, glycemic load and intake of carbohydrates was associated with an increased risk of endometrial cancer among overweight and physically inactive women.

- Alcohol consumption was not associated with risk of endometrial cancer in our study population of Swedish elderly women with generally low alcohol consumption.

- Results from the dose-response meta-analysis on alcohol and endometrial cancer risk suggest a J-shaped relationship. Consumption of alcohol up to 1 drink per day may lower the risk, whereas high consumption, of 2 or more drinks per day, may be associated with a moderate increase in the risk of endometrial cancer.

- Results from the meta-analysis on diabetes and endometrial cancer strongly support an association between type 2 diabetes and endometrial cancer incidence (2-fold increase); do not support an association between diabetes and mortality due to endometrial cancer; suggest a positive association between type 1 diabetes and endometrial cancer.

Seen together, all our observations indicate that insulin-related factors are important in the development of endometrial cancer.
FUTURE RESEARCH

Further prospective studies are needed to confirm the observed inverse association between coffee drinking and risk of endometrial cancer. There is also the necessity to perform studies separating the effect of coffee from that of caffeine. Some studies have shown an even larger protective effect against diabetes from decaffeinated coffee compared to regular coffee, but a recent case-control study on coffee and endometrial cancer observed no association between the two. The effect of tea, which contains many of the compounds thought to be responsible for the postulated association with coffee, also needs to be evaluated.

Further studies elucidating the effect of glycemic load are needed, especially to take into account and separating the effects seen from fiber intake and “healthy behavior”. Larger studies might also have more power to look more closely at subgroups where glycemic load might have a larger impact, as in obese and physically inactive women being at higher risk for insulin resistance and hyperinsulinemia.

In light of the industrialization and urbanization worldwide, which generally tend to increase alcohol consumption, a more recent prospective cohort might be able to clarify in more detail the association patterns between high alcohol intake and endometrial cancer.

There is a great need to evaluate other dietary factors in relation to endometrial cancer, especially in prospective settings, not so prone to recall biases, and fulfilling the time criterion for causality.

Finally, we also need studies taking into account the risk observed in different genetically defined subgroup. This might help explain differences in susceptibility to cancer, as well as give us important clues to the development mechanism and make tailored cancer preventive strategies possible.
SAMMANFATTNING (SUMMARY IN SWEDISH)

Syfte
Forskning har visat att höga insulinivåer är en viktig faktor i uppkomsten av cancer. Diabetes och fetma är sedan länge kända faktorer som är kopplade till höga nivåer av insulin. Även kaffe, kolhydrater och alkohol har visats påverka insulinivåerna. Syftet med avhandlingen är att undersöka kopplingen mellan ovan nämnda kostfaktorer och livmodercancer i en stor svensk kohort. Vi ville också undersöka och bättre precisera sambanden mellan alkohol, diabetes och livmodercancer, varvid två metaanalyser utfördes på redan publicerade artiklar.

Design och metod
I kohortanalyserna användes data från den Svenska Mammografikohorten, en svensk populationsbaserad prospektiv studie innehållande över 60 000 kvinnor och nästan 700 livmodercancerfall. Vi undersökte sambanden med kaffe, kolhydrater och alkohol vid kohortens start 1987-90 och vid uppföljningen 1997 med hjälp av ”Cox proportional hazard-models”. I metaanalyserna identifierades studier med hjälp av databaserna PubMed och Embase samt genom referenslistor från kandidatstudier. Vi summerade de relativa riskerna med 95% konfidensintervall med en ”random effect-model” och i metaanalysen över alkohol och livmodercancer också med en ”dos-response random effect meta-regression-model”.

Resultat

Kaffe och livmodercancer - Artikel I
Resultaten visar att kaffeintag var förknippat med en lägre risk för livmodercancer i kohorten. Kvinnor som drack två koppar kaffe per dag eller mer hade en signifikant lägre risk att drabbas av livmodercancer. Varje kaffekopp bidrog med 10% minskad risk, sett till samtliga kvinnor. Riskminskningen var störst bland överviktiga kvinnor som redan från början har högre risk för livmodercancer. Bland överviktiga bidrog varje kopp kaffe med 12% mindre risk och bland feta handlade det om 20%.

Kolhydrater och livmodercancer - Artikel II
Resultaten visar inget övergripande samband mellan kolhydratintag, glykemiskt index (ett mått på kroppens svar vid kolhydratintag) eller glykemisk load (ett mått som tar hänsyn till det totala svaret vid kolhydratintag, dvs. både kvalitet och kvantitet) och livmodercancer. När vi delade upp materialet och tittade på överviktiga och inaktiva kvinnor fann vi indiker för en ökad risk förknippad med högt kolhydratintag och tre gånger ökad risk för kvinnor med högt glykemisk load.

Alkohol och livmodercancer - Artikel III
Analysen av alkoholkonsumtion i kohorten visade inte något samband med risk för livmodercancer. Resultatet såg likadant ut oavsett ålder, BMI, folsyraintag eller användande av hormonpreparat i klimakteriet.
Metaanalys Alkohol och livmodercancer - Artikel IV
I analyser av sju prospektiva kohorter inkluderande 1 478 663 kvinnor och 5881 livmodercancerfall fann vi ett J-format samband mellan alkoholintag och risk för livmodercancer. Ett måttligt alkoholintag var associerat med minskad risk för livmodercancer, medan vi fann en ökad risk bland kvinnor som drack mer än två drinkar per dag (1 drink ≈ 330ml öl, 150ml vin eller 45ml sprit). Jämfört med personer som inte drack alkohol så var risken för livmodercancer minskad med 6% (95% CI 0.90-0.98) bland de som drack upp till 0.5 drinkar per dag och 10% (95% CI 0.83-0.98) bland de som drack 0.5 - 1 drink och ökad med 16% (95% CI 0.98-1.38) bland de som drack 2 - 2.5 drinkar per dag och 27% (95% CI 1.02-1.60) bland de som drack mer än 2.5 drinkar per dag.

Metaanalys Diabetes och livmodercancer - Artikel V
Analyser av 16 studier innehållandes 96 003 deltagare och 7596 livmodercancerfall visade att förekomst av diabetes var statiskt signifikant associerat med en ökad risk för livmodercancer, (summerat RR 2.10 95% CI 1.75-2.53). Effektberäkningen var något starkare bland fallkontrollstudier (RR 2.33 95% CI 1.87-2.90) än bland kohortstudier (RR 1.62 95% CI 1.21-2.16), starkare bland studier som bara kontrollerade för ålder (RR 2.74 95% CI 1.87-4.00) jämfört med studier med justering (RR 1.92 95% CI 1.58-2.33), och något lägre bland studier som var gjorda i USA än de som kom från Europa. Analys av två mortalitetsstudier fann ett summerat RR 1.58 (95% CI 0.94-2.66) för diabetes och dödlighet i livmodercancer.

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