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# **DIABETES, PHYSICAL ACTIVITY AND ENDOMETRIAL CANCER**

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*Till Pappa*

## ABSTRACT

Accumulating evidence suggests that hyperinsulinemia, in the context of insulin resistance, is associated with carcinogenesis. Physical activity is involved in the regulation of metabolic and hormonal pathways and is an important factor affecting hyperinsulinemia, insulin resistance and body weight.

The major modifiable determinants of insulin resistance, hyperinsulinemia, and diabetes such as obesity, and physical activity, have also been shown to be risk factors for endometrial cancer. No previous studies have investigated whether physical inactivity is a modifier of the association between diabetes and risk of endometrial cancer. No previous study has evaluated a combined effect of diabetes, obesity and physical inactivity as a predictor of endometrial cancer risk. No previous meta-analysis of diabetes and endometrial cancer risk has been performed. Moreover no previous study has investigated the effect of leisure time physical inactivity directly on endometrial cancer risk.

In the first study, we examined the association between diabetes and incidence of endometrial cancer in the Swedish Mammography Cohort. Given that the effect of diabetes may vary by risk factors for endometrial cancer we also examined the potential effect modification by obesity and physical activity. In this population-based prospective cohort of 36 773 women, 225 incident endometrial adenocarcinoma cases were diagnosed between 1997 and 2005. The relative risk (RR) for endometrial cancer among women with diabetes compared to non diabetic women was 1.94, 95% CI =1.23 to 3.08. Obese diabetics with low physical activity had a RR = 9.61, 95% CI=4.66 to 19.83, compared to non-obese, non-diabetic women with high physical activity.

In the meta-analysis, we identified 16 studies (3 cohort and 13 case-control studies), and found that diabetes was statistically significantly associated with an increased risk of endometrial cancer incidence, (summary RR = 2.10 95% CI= 1.75-2.53). Analysis of 2 studies of mortality found a summary RR= 1.58 95% CI 0.94-2.66 for diabetes and endometrial cancer mortality.

In the third study, we investigated the association of total physical activity and different types of physical activity with risk of endometrial cancer in the Swedish Mammography Cohort. After exclusions due to some missing physical activity estimates 33 723 women and 199 endometrial cancer cases were included in the analysis. Relative risks (RR) for endometrial cancer comparing the second to fourth quartiles of total physical activity to the lowest one were 0.80 (95% CI 0.54-1.18); 0.87 (95% CI 0.59-1.28); 0.79 (95% CI 0.53-1.17) respectively. High leisure time inactivity (watching TV/sitting 5 hours or more a day) compared to low was associated with increased risk of endometrial cancer RR=1.66 (95% CI 1.05-2.61).

We observed a statistically significant association between diabetes and endometrial cancer in our cohort, particularly among obese and physically inactive participants. Results from the meta-analysis (which included our results) support a relationship between diabetes and increased risk of endometrial cancer incidence. The similar point estimates from the cohort analysis and meta-analysis suggest that diabetes may be associated with a two-fold increased risk of endometrial cancer.

Total physical activity was only weakly associated with a decreased risk of endometrial cancer, although leisure time inactivity was statistically significantly associated with increased risk for endometrial cancer.

These findings support general health recommendations to reduce obesity and increase physical activity.

## LIST OF PUBLICATIONS

- I. Emilie Friberg, Christos S. Mantzoros, and Alicja Wolk. Diabetes and Risk of Endometrial Cancer: a Population-Based Prospective Cohort Study. Conditionally accepted in *Cancer Epidemiology, Biomarkers & Prevention*
  
- II. Emilie Friberg, Nicola Orsini, Christos S. Mantzoros, and Alicja Wolk. Diabetes Mellitus and Risk of Endometrial Cancer: A Meta-Analysis. Submitted
  
- III. Emilie Friberg, Christos S. Mantzoros, Alicja Wolk. Physical activity and risk of endometrial cancer: a population-based prospective cohort study. *Cancer Epidemiology, Biomarkers & Prevention* 2006;15(11): (in press)

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## LIST OF ABBREVIATIONS

BMI	Body Mass Index
CI	Confidence Interval
IGF	Insulin-like Growth Factor
IGFBP	Insulin-like Growth Factor Binding Protein
MET	Metabolic Equivalent
OC	Oral Contraceptives
PA	Physical Activity
PMH	Postmenopausal Hormone
RR	Relative Risk
SHBG	Sex Hormone Binding Globulin



# 1 BACKGROUND

## 1.1 INTRODUCTION

Endometrial cancer is the fourth most common cancer among women in Westernized countries and the sixth most common 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.

The human body is made for moving and we are essentially maladjusted to our sedentary lifestyle. The promotion of a physically active lifestyle is an increasingly important public health objective, which can impact on many health outcomes. Studies have shown low levels of physical activity to be associated with hyperinsulinemia, obesity, diabetes and all cause mortality. Over the years it has become evident that hyperinsulinemia, in the context of insulin resistance, is associated with carcinogenesis. Epidemiologic studies have observed an elevated risk of endometrial cancer in relation to hyperinsulinemia. The major modifiable determinants of insulin resistance, hyperinsulinemia, and diabetes are obesity, and physical activity.

In light of this, we wanted to assess a number of unanswered questions; evaluate whether physical inactivity modifies the association between diabetes and risk of endometrial cancer; evaluate the combined effect of diabetes, obesity and physical inactivity as a predictor of endometrial cancer risk; evaluate the effect of leisure time physical inactivity directly as well as the effect of total physical activity on endometrial cancer risk. Furthermore we wanted to provide a more precise point estimate of the association between diabetes and endometrial cancer incidence.

## 1.2 ENDOMETRIAL CANCER

### 1.2.1 Incidence and trends

Endometrial cancer is the fourth most common cancer among women in Western Europe, United States and Canada, and the sixth worldwide (1). The lowest rates can be found in Asia and India. The incidence is ten times higher in North America and Europe compared to less developed countries and the incidence is increasing when life expectancy rises (2). This difference in incidence rates suggests that diet and other lifestyle factors may be important for the risk of developing this malignancy.

Around 1200 women are diagnosed with endometrial cancer in Sweden every year, with an incidence of 27.3 per 100 000. A majority of the women are diagnosed after the age of 55 years. Fortunately, the prognosis for survival is high at least in westernized countries; the 5-year survival in Sweden is over 80% (3).

### 1.2.2 Histopathology

Endometrial cancer is the most common cancer of the uterine body (corpus uteri). The majority (80%) is of endometrioid adenocarcinoma histological type, followed by seropapillary adenocarcinoma, clear-cell adenocarcinoma and endometrioid adenocarcinoma with squamous differentiation (2).

Some authors have argued that endometrial cancer can be divided into two different diseases: Type I or endometrioid and Type II or non-endometrioid (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. The Type II may develop without hyperplasia and thus estrogenic stimulation is not likely to be as important (2). Unfortunately most studies do not distinguish between these tumor subtypes.

### 1.2.3 Risk Factors

#### 1.2.3.1 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 (3).

#### 1.2.3.2 Estrogen and progesterone

Sex steroid hormones are essential for the growth, differentiation and function of many tissues in both men and women. Estrogens are produced by the ovary in premenopausal women. Progesterone is produced by the ovary, adrenal glands and in the brain. In menopausal women, the ovarian production of estrogens and progesterone falls to very low levels. After menopause, the principal estrogen is produced by peripheral aromatization of androstenedione within adipose tissue.

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 (4). 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 (5). Indeed, each of the reproductive factors that influences long term exposure to high estrogen and to low progesterone levels, such as early age at menarche, late age at menopause, null parity, no use of oral contraceptives, and use of unopposed hormone replacement therapy, has been shown to be associated with risk of endometrial cancer (6-24).

Sex Hormone Binding Globulin (SHBG) is a globulin that is mainly produced by the liver, and that specifically binds 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 (25).

#### 1.2.3.3 Body mass

Obesity in adulthood has consistently been associated with an increased risk of endometrial cancer among both pre and postmenopausal women (25). 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 (26-28), and/or 2) decreasing production of SHBG (29). However, the primary proposed explanation theorizes that high adiposity has also been shown to decrease progesterone levels through increasing the numbers of anovulatory cycles (30).

Obesity is also associated with insulin resistance and hyperinsulinemia (31-33), which may increase endometrial cancer risk through estrogenic or growth factor pathways.

#### 1.2.3.4 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. At the extreme, insulin resistance may cause glucose intolerance and lead to the development of type 2 diabetes. A

number of epidemiologic studies have reported on associations between diabetes and endometrial cancer see Table 1-3 in Paper II.

Elevated insulin concentrations and decreased glucose tolerance are associated with obesity. The relationship between BMI and fasting insulin levels is continuous and linear (25). 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. Independently of the effect on excess body fat, lack of physical activity may also contribute to the development of insulin resistance.

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 a regulator of availability of sex-steroids 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 (25).

Hyperinsulinemia may increase levels of free estrogen through decreasing concentrations of circulating SHBG (34, 35). Furthermore, hyperinsulinemia through decreasing levels of IGFBP-1 and IGFBP-3 increases circulating free IGF-1, which by binding and activating IGF-1 receptors in the endometrium stimulates cell proliferation (36-40).

#### *1.2.3.5 Adiponectin*

Adiponectin is an adipose tissue derived endogenous insulin sensitizer which is decreased in obesity. It has recently been reported that hyperinsulinemia is closely associated with lower circulating levels of adiponectin (41). It has been shown that low adiponectin levels are associated with low levels of physical activity (42, 43), higher levels of body fat and visceral tissue (33), higher concentrations of circulating estradiol (44), and increased endometrial cancer risk (45).

#### *1.2.3.6 Physical activity*

A number of epidemiologic studies have reported on associations between different physical activities and incidence of endometrial cancer (46-61) (Table 1). Most studies have shown some aspect of physical activity to be inversely associated with endometrial cancer risk.

The proposed mechanism for the protective effect relates lower levels of endogenous estrogen among physically active women (62, 63). Physical inactivity is a major determinant of body weight and may shift the body composition toward more body fat and visceral tissue. Physical inactivity has also been shown to affect insulin resistance and hyperinsulinemia not only through obesity but also directly, furthermore physical activity has been shown to promote insulin sensitivity (64, 65).

## Physical activity table references

## Physical activity table references

#### *1.2.3.7 Diet*

According to the World Cancer Research Fund and American Institute of Cancer Research (66) the effect of dietary factors, besides energy and factors leading to obesity, is insufficiently studied to permit any conclusions.

#### *1.2.3.8 Cigarette smoking*

A protective effect of cigarette smoking on endometrial cancer risk was suggested as early as 1980 (67). Since then a number of epidemiologic studies have confirmed the reduced risk (13, 67-71). The inverse association of cigarette smoking with endometrial cancer risk may relate to the fact that female smokers have similar 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.(72).

#### *1.2.3.9 Genetic susceptibility*

Data indicate that endometrial cancer may occur in genetically susceptible individuals. One usually estimates 5% of the cases to be hereditary (3). Data on familial aggregation reflecting clustering of either sporadic or hereditary cases is however scarce.

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. The p53 gene and genes involved in cellular differentiation and proliferation have also been studied (73). 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 hormonal carcinogenesis.

## 2 AIMS

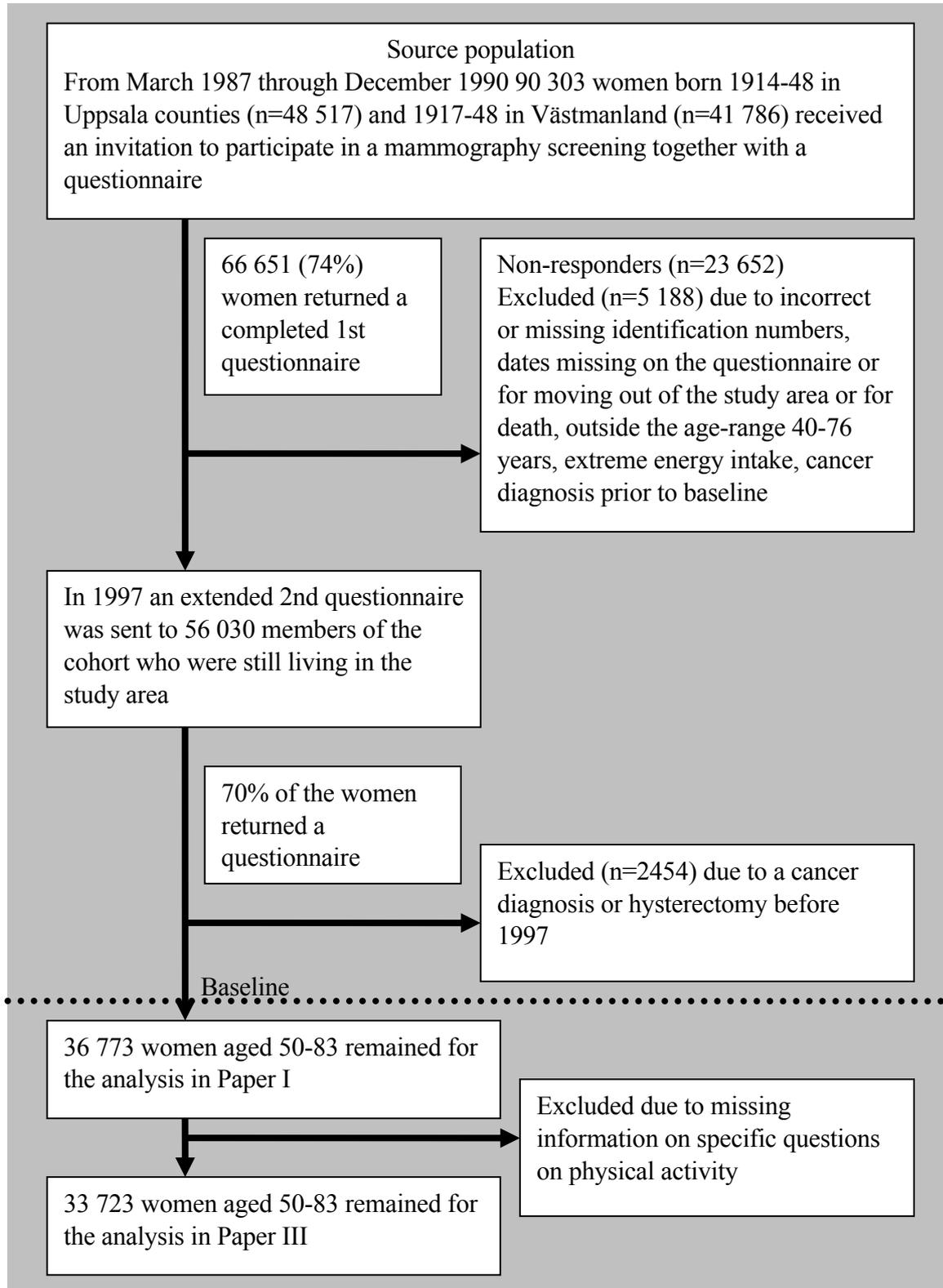
- To evaluate the risk for endometrial cancer development associated with diabetes among women in the Swedish Mammography Cohort.
- To evaluate a potential effect modification by body mass index and physical activity on the association between diabetes and endometrial cancer incidence.
- Using a meta-analysis to quantitatively summarize the accumulated evidence in the association between diabetes and risk for endometrial cancer.
- To evaluate the evidence for an association between diabetes and endometrial cancer mortality and type 1 diabetes and endometrial cancer.
- To evaluate the risk for endometrial cancer incidence associated with total physical activity among women in the Swedish Mammography Cohort.
- To evaluate the effect of different types of physical activity on the risk of endometrial cancer among women in the Swedish Mammography Cohort.

### 3 SUBJECTS AND METHODS

#### 3.1 THE SWEDISH MAMMOGRAPHY COHORT STUDY (PAPER I AND III)

##### 3.1.1 Cohort population

Figure 1. Study population



### 3.1.2 Exposure assessment, case ascertainment and follow up.



SMC 87 questionnaire

SMC 97 questionnaire

*Exposure information used in the cohort analysis came from the SMC-questionnaires.*

The self-administered SMC 87 questionnaire used in the SMC solicited information on diet, weight, height, educational level, parity, age at first birth, and family history of breast cancer. Diet was assessed with a food-frequency questionnaire that included 67 food items. Women chose from eight predefined frequency categories, ranging from never/seldom to four or more times per day. We used age-specific (<53, 53-65, >65 years) portion sizes that were based on mean values obtained from 213 randomly-chosen women from the study area whose food intake for 5922 days was weighed and recorded (Wolk A: unpublished data).

The updated and extended SMC 97 questionnaire included information on weight at different ages (including birth weight), height, long-term physical activity, smoking status and history, educational level, marital status, reproductive factors, family history of cancer and myocardial infarction, use of some medications (e.g., aspirin), alcohol, detailed diet etc. The 1997 questionnaire elicits information on usual consumption of 96 foods/food groups during the past year as well as use of dietary supplements during the previous 10 years.

Diabetes were self-reported on the SMC 97 questionnaire and assessed with the question “have you ever been diagnosed with diabetes”. For women with diabetes who were hospitalized, information was also obtained or confirmed by linkage to the Swedish In-patient Registry. Naturally, there was a big overlap between the two exposure assessing methods; 1528 women answered that they had a diagnosis of diabetes on the questionnaire and we only found 100 additional women from the In-patient Registry.

Body mass index was calculated as weight in kg divided with the square of the length in meters (BMI, kg/m<sup>2</sup>). The validity for self-reported weight and height as compared to measurements in Swedish women is high (Pearson correlation coefficient = 0.9 and 1.0 respectively (74)). Education was assessed with six questions ranging from 6 years of basic education to university studies. Cigarette smoking was measured as pack-years history of smoking. Total energy, fruit and vegetable intake were assessed with the use of the self-administered food-frequency questionnaire.

Estimated total physical activity was based on five types of activities defined as home/household work, walking/cycling, work/occupation, TV/reading, and exercise (Figure 2), and measured as multiples of the metabolic equivalent (MET, kcal·kg<sup>-1</sup>·h<sup>-1</sup>) (Table 2). The physical activity questions were validated by comparing with two 1-week records; Spearman correlation coefficient was 0.7 (75).

**Figure 2. Physical activity questionnaire.**

Mark your level of physical activity **at different ages:**

<b>Home/household work</b>	15 yrs	30 yrs	50 yrs	this yr
Less than 1 hour/day	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
1-2 hours/day	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3-4 hours/day	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5-6 hours/day	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
7-8 hours/day	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
More than 8 hours/day	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

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<b>Walking/cycling</b>	15 yrs	30 yrs	50 yrs	this yr
Hardly ever	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Less than 20 min/day	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
20-40 minutes/day	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
40-60 minutes/day	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
1-1,5 hours/day	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
More than 1,5 hours/day	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

---

<b>Work/occupation</b>	15 yrs	30 yrs	50 yrs	this yr
Mostly sitting down	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Sitting down half the time	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Mostly standing up	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Mostly walking, lifts, carry <u>little</u>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Mostly walking, lifts, carry <u>much</u>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Heavy manual labour	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

**Leisure time**

<b>Watching TV/reading</b>	15 yrs	30 yrs	50 yrs	this yr
Less than 1 hour/day	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
1-2 hours/day	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3-4 hours/day	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5-6 hours/day	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
More than 6 hours/day	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

**Exercise**

Less than 1 hour/week	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
1 hour/week	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2-3 hours/week	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4-5 hours/week	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
More than 5 hours/week	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

11. How many hours in 24 hours do you usually...

Sleep  hours/  
24 hours

hours/  
24 hours

**Table 2. Types of physical activities with assigned mean MET values and correlation coefficients.**

Activity		MET/h	r*
Home/ household work		2.5	0.8
Walking/cycling		3.6	0.4
Work/occupation	Mostly sitting	1.3	0.5
	Sitting down more than half of the time	1.8	
	Mostly standing	2.2	
	Doing lifts	2.6	
	A lot of lifts	3.0	
	Heavy labor	3.9	
Leisure time	Leisure time activity	5.0	0.2
	Leisure time inactivity	1.2	0.6
Sleeping		0.9	

\* Spearman correlation coefficient

### 3.1.2.1 Case Ascertainment and Follow-up

By linkage of the cohort with the Swedish Cancer Registry through July 1, 2003 and with the Regional Cancer Registry in the study area through June 30, 2005, we identified 225 adenocarcinoma endometrial cancer cases.

Furthermore, by linkage with the nationwide Swedish In-patient Registry, we identified women who had a hysterectomy for reasons other than endometrial cancer.

Dates of death or migration from the study area were ascertained through the Swedish Death Register and the National Swedish Population Register, respectively.

Of the 39 227 women who responded to the SMC 97 questionnaire, we excluded those diagnosed with cancer (other than non-melanoma skin cancer) and those having had a hysterectomy before returning the questionnaire. After these exclusions, 36 773 women aged 50 to 83 years remained. For the analysis of physical activity, we further excluded women with missing information on specific questions regarding different types of physical activities. After these exclusions 33 723 women including 199 endometrial cancer cases remained.



Swedish Cancer Registry

Regional Cancer Registry

National Swedish Population Register

Swedish Death Register

Swedish In-patient Registry

*Case ascertainment and follow-up were made by linkages with different registries in Sweden.*

### **3.1.3 Statistical analysis – Paper I**

In 36 773 women among who 225 endometrial cancer cases were identified we estimated the risk of endometrial cancer using Cox proportional hazards model. We calculated person-years of follow-up for each woman from the date of return of the questionnaire in 1997 to the date of an 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 30 June 2003 – 30 June 2005, or the end of follow-up June 30, 2005, whichever came first. The RRs of endometrial cancer (with 95% CIs), both age and multivariable adjusted, were calculated by dividing the incidence rate among diabetic women with that among non-diabetic women. We conducted analyses stratifying by BMI and physical activity. Further we examined the combined effect of diabetes and BMI or physical activity and by the combined categories of diabetes, BMI and physical activity. The statistical significance of interactions was tested by adding an interaction term to the Cox model, simultaneously containing the main variables and the age in months.

### **3.1.4 Statistical analysis – Paper III**

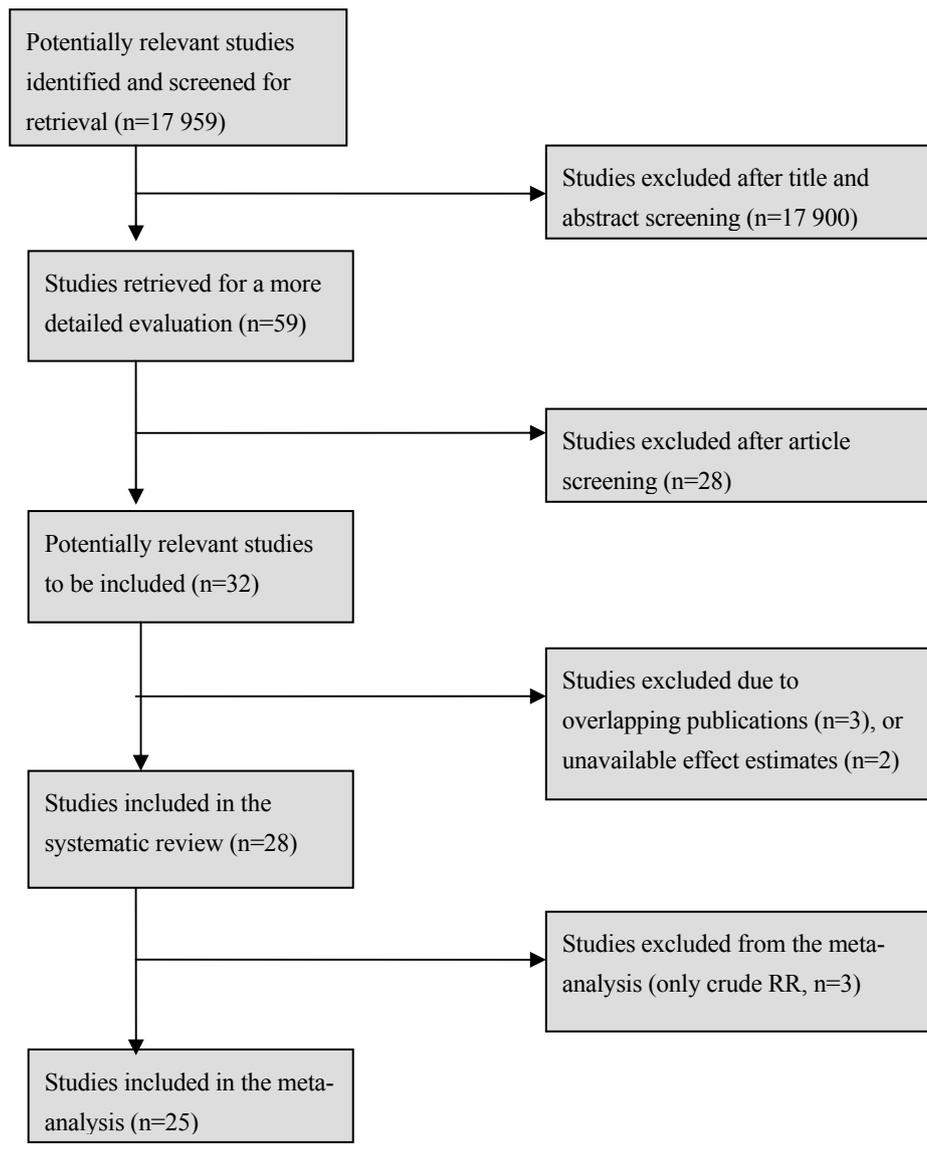
In the analysis of 33 723 women including 199 endometrial cancer cases we estimated the risk of endometrial cancer using Cox proportional hazard model. We calculated person-years of follow-up in the same way as in Paper 1. The RRs of endometrial cancer (with 95% CIs) were calculated by dividing the incidence rates among women in the three upper quartiles of total physical activity with women in the lowest quartile of total physical activity. We calculated the RR of endometrial cancer (with 95% CI) for different components of physical activity (occupational physical activity, household work, walking/bicycling, leisure time activity), or inactivity (watching TV/sitting) by dividing the incidence rate among women with a high level of activity or inactivity with women with low level of activity or inactivity. We performed age-adjusted and multivariable analyses. Additionally stratified analyses were conducted by BMI ( $\leq 27$  kg/m<sup>2</sup> vs  $> 27$  kg/m<sup>2</sup>).

## **3.2 META-ANALYSIS (PAPER II)**

### **Search Strategy**

We identified studies by a literature search of the Medline database (from January 1, 1966, through August 31, 2006) 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 3. Study selection progression**



**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. From each study, we extracted the risk estimates that reflected the greatest degree of control for potential confounders.

## **Statistical Analysis – Paper II**

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 (76) 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  $I^2$  statistic (77). Publication bias was assessed by constructing a funnel plot (78), and by Egger's regression asymmetry test (79).

For cohort and case control studies that reported incidence rate ratios, we conducted subgroup meta-analyses to examine potential sources of heterogeneity, including study design, and hospital vs population based case-control studies.

## 4 RESULTS

### 4.1 DIABETES AND ENDOMETRIAL CANCER RISK (PAPER I)

During follow-up of 36 773 women in the cohort, 225 endometrial cancer cases were identified. The mean age at diagnosis of endometrial cancer was 68.6 ( $\pm$  9.5) years. Individuals diagnosed with diabetes were older and heavier than non-diabetics, had a little lower total physical activity and less education, and tended to have used less postmenopausal hormone treatment and oral contraceptives. Overall diabetes was positively associated with endometrial cancer risk in both age-adjusted and in multivariate analyses adjusting for confounders, such as BMI and total physical activity (Table 3).

**Table 3. Associations of Diabetes with RR of Endometrial Cancer**

	No of cases	Person-years	RR (95% CI)*	RR (95% CI)†
No diabetes	203	254 760	1.0 (ref)	1.0 (ref)
Diabetes	22	10 887	2.37 (1.51-3.74)	1.94 (1.23-3.08)

\* *Adjusted for age (in months).*

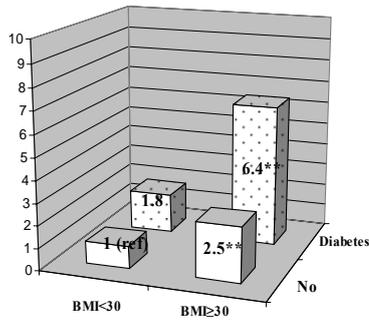
† *Adjusted for age (in months), BMI (continuous) and total physical activity (MET/hour quartiles <38.8, 38.9-42.1, 42.2-45.8, 45.9+).*

We also examined whether the association with diabetes was more pronounced in women with high BMI and among those with low physical activity (defined as the lowest tertile of total physical activity). Women who were obese (BMI $\geq$ 30 kg/m<sup>2</sup>) and had diabetes had an almost 3-fold increased risk comparing with those with the same BMI but without diabetes. Similarly, women classified as having low physical activity had almost 3-fold increased risk if they had diabetes.

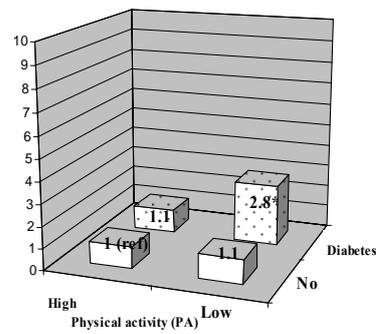
In the analysis using as a reference group non-diabetic non-obese woman, women with diabetes and high BMI ( $\geq$ 30 kg/m<sup>2</sup>) had more than a 6-fold increased risk ( $P_{\text{interaction}}=0.25$ ). When examining the effect of diabetes and total physical activity, the excess risk for endometrial cancer associated with diabetes was statistically significantly 3-fold higher in the low activity group as compared to non-diabetic women in the high physical activity group ( $P_{\text{interaction}}=0.002$ ). We also examined combined effect of diabetes, BMI and physical activity in relation to endometrial cancer risk, dividing the subjects according to the same cut-off points as in the above analyses. Diabetes in women with high BMI and low total physical activity was associated with almost 10-fold increased risk as compared to non-diabetic women with low BMI and high physical activity (Figure 4).

**Figure 4. Diabetes and Risk of Endometrial Cancer in Subgroups Defined by BMI and Physical Activity**

**A.** Diabetes and risk of endometrial cancer stratified by BMI.



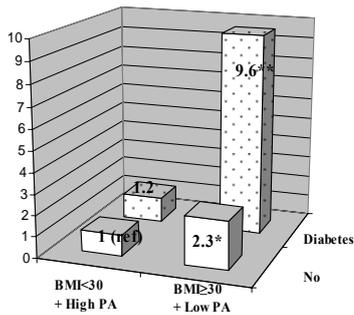
**B.** Diabetes and risk of endometrial cancer stratified by physical activity.



Adjusted for age (in months) and total physical activity (MET/hour quartiles <math><38.8</math>, <math>38.9-42.1</math>, <math>42.2-45.8</math>, <math>45.9+</math>).

Adjusted for age (in months) and BMI (continuous).

**C.** Diabetes and risk of endometrial cancer stratified by the combined effect of BMI and physical activity.



Adjusted for age (in months).

\* $P$ -value <math><0.01</math>

\*\*  $P$ -value <math><0.0001</math>

## **4.2 META-ANALYSIS OF DIABETES (PAPER II)**

### **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 (49, 80-83), and 13 were case-control studies that used odds ratios as the measure of risk (10, 15, 55, 84-93), seven were cohort studies that used standardized incidence and or /mortality ratio as the measure of relative risk (94-100).

In the primary meta-analysis of diabetes and endometrial cancer incidence, we included three cohort studies that reported incidence rate ratios (49, 80, 83) and 13 case-control studies (10, 15, 55, 84-93). These 16 studies included a total of 96 003 participants. The 4 cohort studies (94, 96-98) that reported standardized incidence ratios were analyzed separately.

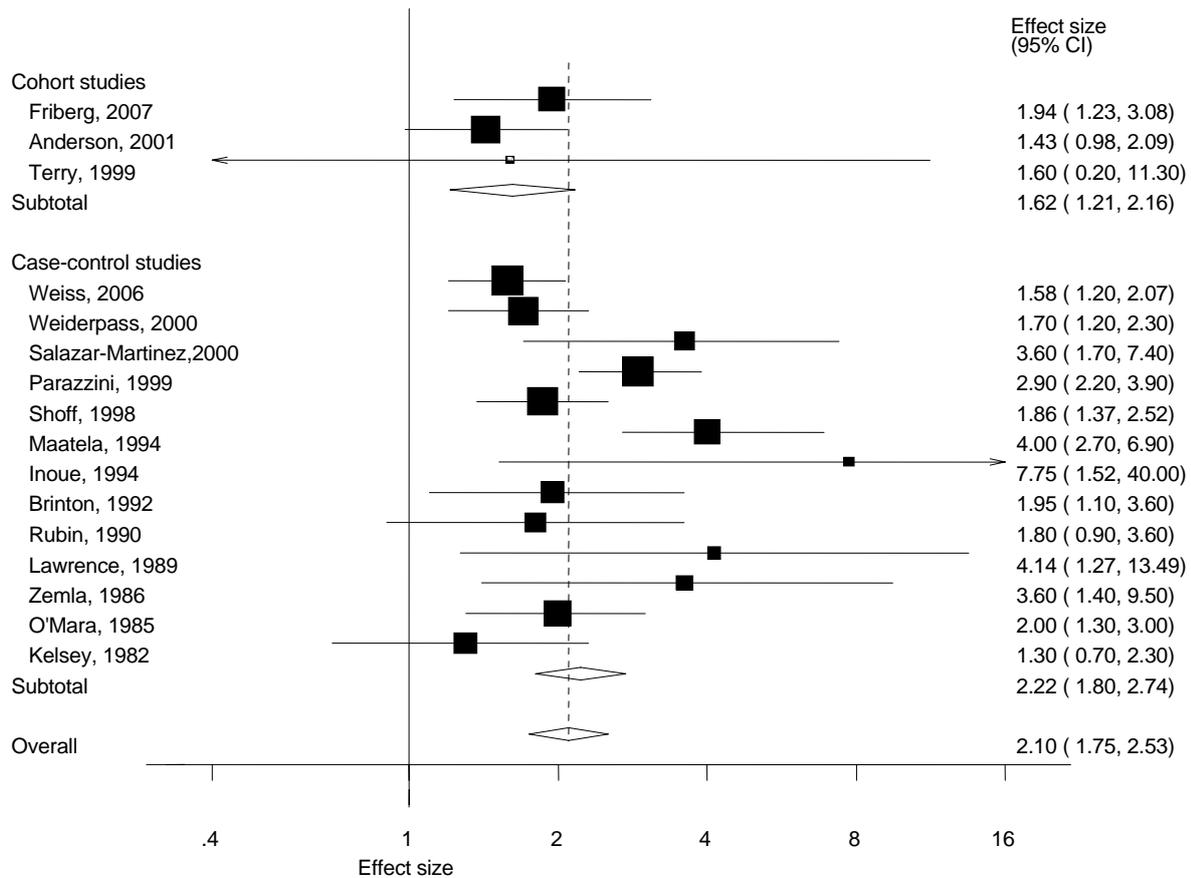
For the meta-analysis of diabetes and endometrial cancer mortality, we included the two cohort studies that reported mortality rate ratios (81, 82). These two studies enrolled a total of 896 participants. The 4 cohort studies (94, 96-98) that reported standardized incidence ratios and the 3 cohort studies (94, 99, 100) that reported standardized mortality ratios were analyzed separately.

Three studies reported on type 1 diabetes and incidence of endometrial cancer, one case control study (84) and two studies providing standardized incidence ratios (94, 95). One study reported on type 1 diabetes and endometrial cancer mortality providing a standardized mortality ratio including only one case of endometrial cancer (94).

### **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 5. 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 5. 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. RR= relative risk; CI= confidence interval; 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. All statistical tests were two-sided. Statistical heterogeneity between studies was assessed with Cochran's Q test.

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 4). 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 4. Summary relative risk (RR) estimates and 95% confidence intervals (CI) for case-control and cohort studies of the association between diabetes and endometrial cancer incidence by study design, geographical area and adjustments.**

Subgroup	No. of studies	Summary RR (95% CI)
Study design		
Cohort studies	3	1.62 (1.21-2.16)
Case-Control	13	2.22 (1.80-2.74)
Population based	7	2.04 (1.58-2.63)
Hospital based	6	2.51 (1.78- 3.56)
Geographical area		
United States	8	1.70 (1.47-1.98)
Europe	6	2.51 (1.83-3.45)
Other	2	4.10 (2.09-8.01)
Adjustments		
Full	11	1.92 (1.58-2.33)
Age	5	2.74 (1.87-4.00)

A positive association was observed between diabetes and endometrial cancer incidence in the cohort studies that reported standardized incidence ratios (94, 96-98) (summary RR=1.63 95% CI 1.30-2.05; test for heterogeneity  $Q=9.60$ ;  $p=0.02$ ;  $I^2=8.8\%$ ).

#### **Endometrial Cancer Mortality**

Of the two cohort studies of diabetes and mortality from endometrial cancer (81, 82), One (81) reported a statistically significant positive association, and one (82) 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 (94, 99, 100) (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 (84, 94, 95). 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  $Q=6.66$ ;  $p=0.04$ ;  $I^2=70.0\%$ ).

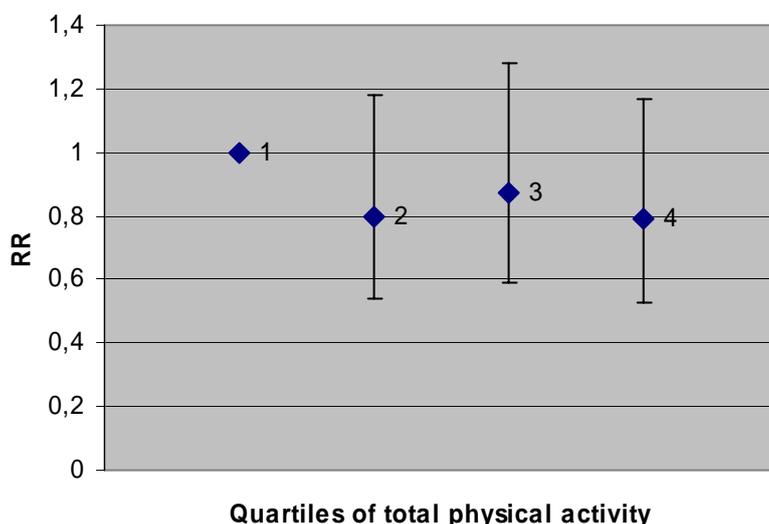
#### **Publication Bias**

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).

### 4.3 PHYSICAL ACTIVITY AND ENDOMETRIAL CANCER (PAPER III)

During follow-up of 33 723 women in the cohort 199 endometrial cancer cases were diagnosed. At baseline 48.2% of the women were working. Women with a low level of total physical activity were older, had higher BMI, larger percent of them reported history of use of oral contraceptives and postmenopausal hormones, they had lower energy intake and lower consumption of fruit and vegetables and higher frequency of diabetes than women with a higher level of total physical activity. Overall physical activity was inversely, albeit not significantly, associated with endometrial cancer risk in both age-adjusted and multivariate analyses, RR for endometrial cancer risk was; second to fourth quartile of total physical activity as compared to the lowest one 0.80 (95% CI 0.54-1.18); 0.87 (95% CI 0.59-1.28); 0.79 (95% CI 0.53-1.17) respectively (Figure 6).

**Figure 6. Total physical activity and risk for endometrial cancer**



*Q1 < 38.9, Q2 38.9-42.2, Q3 42.2-45.9, Q4 ≥ 45.9 (MET/h)*

*Rate ratios from Cox proportional hazards models (RRs) and 95% CIs of endometrial cancer adjusted for age in months, parity (0, 1-2, 3+), history of diabetes (yes/no), total fruit and vegetable (intake in quartiles <239g, 239g-344g, 345g-482g, 483g+), education, and BMI (<20, 20-25, 26-30, 30+ (kg/m<sup>2</sup>))*

We further investigated the associations between specific types of physical activity and endometrial cancer risk. Table 5 shows that leisure time inactivity (i.e. watching TV/sitting 5 hours or more a day) was associated with a statistically significantly 66% increased risk of endometrial cancer. In contrast, walking/bicycling at least 1 hour a day was associated with a non-significantly decreased risk. Occupational activity, household work and leisure time activity were not associated with endometrial cancer risk (Table 5).

**Table 5. Associations of physical activity (PA) with Rate ratios (RRs) and 95% CIs of endometrial cancer for 33 723 women in the Swedish Mammography Cohort**

Variable	PA	No of cases	RR (95% CI) *
Work/Occupation†	Low	109	1.00
	High	90	1.01 (0.75-1.37)
Household work‡	Low <5h/d	139	1.00
	High ≥5h/d	60	0.99 (0.71-1.38)
Walking/Bicycling § (mainly for transportation)	Low <1h/d	175	1.00
	High ≥1h/d	24	0.71 (0.45-1.10)
Leisure time activity § (including exercise)	Low <20 min/d	99	1.00
	High ≥20min/d	100	0.99 (0.73-1.32)
Leisure time inactivity § (watching TV/sitting)	Low <5h/d	175	1.00
	High ≥5h/d	24	1.66 (1.05-2.61)

\* Rate ratios from Cox proportional hazards models adjusted for age in months, parity (0, 1-2, 3+), history of diabetes (yes/no), total fruit and vegetable (intake in quartiles <239g, 239g-344g, 345g-482g, 483g +), education, BMI (<20, 20-25, 26-30, 30+ (kg/m<sup>2</sup>), and work/occupation, walking/bicycling, household work, leisure time activity, leisure time inactivity (watching TV/sitting) simultaneously.

† High: mostly standing up, doing lifts, a lot of lifts, and heavy labor; Low: mostly sitting down and sitting down more than half of the time.

‡ High level was defined as the > 50<sup>th</sup> percentile in the cohort.

§ High level was defined as the > 75<sup>th</sup> percentile in the cohort.

We also examined whether the observed associations differed according to BMI status, by stratifying the cohort into groups with BMI ≤ 27 kg/m<sup>2</sup> and BMI > 27 kg/m<sup>2</sup>. We observed no significant differences between the two groups. Furthermore, we compared the most inactive women (5 hours of inactivity at leisure time or more a day) who simultaneously had a low level (below the median) of all other activities (i.e. work/occupation, household work, walking/bicycling and leisure time activity) with the group of physically active women reporting a short time of leisure time inactivity and simultaneously a high level of all other activities and observed an increased risk of endometrial cancer (RR=1.63 95%CI 0.97-2.71).

## 5 DISCUSSION

### 5.1 MAIN FINDINGS

#### 5.1.1 Diabetes and endometrial cancer risk (Paper I)

In this population-based prospective cohort study, women with diabetes had a statistically significant 2-fold higher risk of developing endometrial cancer. This association was independent of confounders such as obesity and physical activity. Importantly, the risk was strong among obese diabetic women compared to non-obese women without diabetes (6-fold increased risk), and among diabetics with low levels of physical activity compared to women without diabetes and a high level of total physical activity (3-fold increased risk). Participants with the most unfavorable combination of diabetes with both a high BMI and reporting low physical activity had almost 10-fold higher risk in comparison to non-diabetic, non-obese women who reported high physical activity.

This is the first prospective cohort study showing diabetes to be statistically significantly associated with an increased risk of endometrial cancer. These results are in agreement and expands findings from case-control studies (55, 84-86, 101). Although two previous cohort studies suggested a positive overall association with endometrial cancer incidence (multivariate RR 1.43, 95% CI 0.98-2.1) (80) as well as mortality (1.33, 95% CI 0.92-1.90) (82), the results did not achieve statistical significance. Our observation that the risk seems to be more pronounced among obese diabetic women is in accordance with the results from three previous case-control studies (55, 85, 86) and one cohort study (80). Furthermore, we have shown for the first time that the association between diabetes and endometrial cancer may be significantly modified by physical activity. Physically inactive and obese diabetic subjects have a 9.6 times higher risk for endometrial cancer compared to non-diabetic, non-obese women who reported high physical activity. .

#### 5.1.2 Meta-analysis (Paper II)

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 ratio.

### **5.1.3 Physical activity and endometrial cancer risk (Paper III)**

In this prospective cohort study, we found that leisure time inactivity (watching TV/sitting 5 hours or more a day) was statistically significantly associated with an increased risk of endometrial cancer incidence. Total physical activity and walking/bicycling were associated with a non significant decreased risk. We have not observed associations with occupational, household work or leisure time activity. The associations were not modified by BMI.

To our knowledge, leisure time inactivity in relation to endometrial cancer risk has not been directly investigated previously. However, the observed increased risk of endometrial cancer among women being inactive during leisure time indirectly supports previous studies showing a statistically significant inverse association with high levels of leisure time physical activities (which might also reflect a low level of inactivity) (46, 49, 52-54, 58, 59, 61). Our results agree with the only other prospective cohort study that investigated total physical activity (covering 24 hours) and risk of endometrial cancer and reported a similar magnitude of risk (RR=0.8, 95% CI 0.6-1.0) (47). The apparent lack of an inverse association between leisure time activities in our study may be due to a lower validity of this question than our other physical activity questions (Table 2), and possibly a low validity in previous studies not showing an association (48, 56, 60).

## **5.2 METHODOLOGICAL CONSIDERATION**

This thesis includes two types of studies. Risk of endometrial cancer in relation to diabetes and physical activity (Paper I, III) was investigated in a population-based prospective cohort study. Risk of endometrial cancer in relation to diabetes was further explored in a meta-analysis (Paper II).

### **5.2.1 Precision – absence of random errors**

Precision is defined as absence of random errors. It is estimated by 95% confidence intervals and depends in large on the sample size, the 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-analysis, which also gives us an opportunity to examine consistency.

### **5.2.2 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 and those who should theoretically be eligible for the study, 2) if there are systematic differences in characteristics between those who are selected and those who are not, 3) if there are differences in loss to follow-up.

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 recall or 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 rather 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.

In our meta-analysis, as in all meta-analyses, the possibility of publication bias is of concern, but a formal statistical test and inspection of the funnel plot did not provide evidence for such bias.

### **Information bias**

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

Misclassification of the exposure in the cohort study cannot be ruled out. Since exposure was assessed only once, changes in exposures during the follow-up are possible. Most likely misclassification would lead to attenuation of our results. One limitation of our cohort study is that identification of diabetic women was partly based on self-reports what might lead to underestimation of the true prevalence of diabetes (we found a 4.4% prevalence of diabetes at baseline in our cohort, the prevalence in the whole Swedish population is estimated to be 3-4% (102)). Thus, incomplete identification of diabetic women in the cohort could lead to attenuation of our results. Furthermore we were also unable to distinguish between type 1 and type 2 diabetes but subjects with type 1 diabetes are a distinct minority among adult diabetics in Sweden (0.5% of the diabetics in the Swedish population (102)).

Our meta-analysis must be interpreted in the context of limitations of the available data. Similar to the Swedish Mammography Cohort many studies 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 underdiagnosed 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.

### **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 association between diabetes, physical activity and endometrial cancer (Paper I and III), we adjusted for several established and potential risk factors known to affect risk of endometrial cancer. However, the exposures could be related to some other unknown factor affecting risk which was not controlled for in this study. Thus, neither confounding nor residual confounding can be completely ruled out, and could hypothetically influence our ability to detect an association.

### **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, the result on diabetes and endometrial cancer risk in our cohort study was consistent to results of the meta-analysis.

### **Limited statistical power**

The statistical power 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.

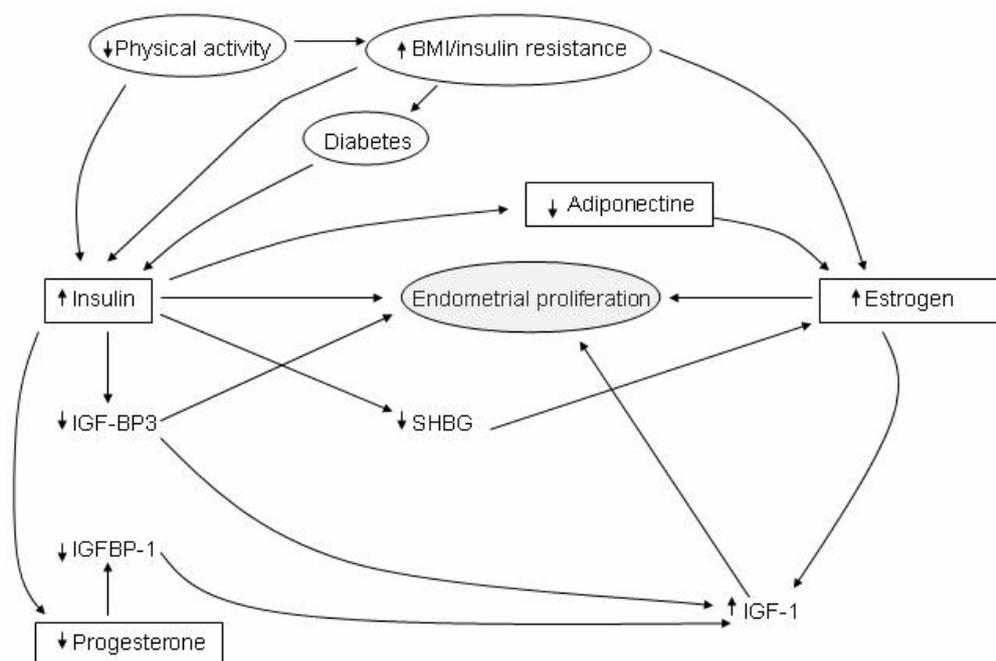
Our meta-analysis findings on endometrial cancer mortality in relation to diabetes, and our data on the risk of endometrial cancer incidence in type 1 diabetes, are limited by uncertainty due to smaller number of studies and studies including small numbers of cases.

## **5.3 GENERAL DISCUSSION**

Most likely several mechanisms are involved in the development of endometrial cancer in women (Figure 7). High levels of insulin is a marker of diabetes, obesity and physical inactivity, and 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 on endometrial cells (103). Hyperinsulinemia may also increase levels of unbound estrogens through decreasing concentrations of circulating SHBG (34, 35). Estrogens have been shown to increase endometrial cancer risk by stimulating proliferation of endometrial cells (4), when unopposed by progesterone (especially in postmenopausal women) (5, 104). High prediagnostic C-peptide concentrations, which is an indication of hyperinsulinemia, and a common feature of diabetes have been associated with an elevated risk of endometrial cancer in epidemiologic studies (105). 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 (95). Finally, hyperinsulinemia by decreasing levels of IGFBP-1 and IGFBP-3 increases circulating free IGF-1, which by binding and activating IGF-1 receptors in the endometrium stimulates cell proliferation (36-40). Furthermore, decreased circulating levels of IGFBP-3 may also have a direct regulatory role in cell growth control and cancer (106, 107).

Adiponectin is an endogenous insulin sensitizer which lies upstream of all the above mentioned hormonal factors and regulates their circulatory levels (33). Low adiponectin levels are not only associated with higher levels of circulating estradiol and hyperinsulinemia/insulin resistance (44), but may also directly alter cell proliferation/apoptosis and angiogenesis (108). Low levels of adiponectin have been shown to predict not only diabetes but also endometrial cancer incidence (109) and can thus be a link between diabetes, hormonal abnormalities and endometrial cancer risk. It has also been observed that lower circulating levels of adiponectin is closely associated with obesity (110).

**Figure 7. Molecular mechanisms affecting endometrial cell proliferation.**



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. The further increased risk observed in obese diabetic women is compatible with the fact that obesity induces both a state of significant hypoadiponectinemia and hyperinsulinemia and an excess of circulating free endogenous estrogens due to an increased estrogen production in peripheral fat tissue (26-28), and/or through a decreased production of SHBG (29). The lack of increased risk observed among physically active diabetics observed in our study on diabetes and endometrial cancer risk may reflect the increased insulin sensitivity found in physically active women (111) and/or a shift in body composition containing less body fat and visceral adipose tissue (31, 32). Less amount of adipose tissue has been associated with higher adiponectin levels and lesser degrees of insulin resistance/hyperinsulinemia (33).

Physical inactivity is a major determinant of body weight and may shift the body composition toward more body fat and visceral tissue. Obesity induces an excess of circulating bioactive endogenous estrogens in peri- and postmenopausal women due to an increased estrogen production from aromatization of androgen in peripheral fat tissue (26-28), and/or through a decreased production of SHBG (29). On the other hand, physically active women have been observed to have lower levels of endogenous estrogen (62, 63). Obesity is also associated with insulin resistance and hyperinsulinemia (31-33). Physical inactivity has also been shown to affect insulin resistance and hyperinsulinemia (64, 65) not only through obesity but also directly, and physical activity has been shown to promote insulin sensitivity (111, 112). Low adiponectin levels have been associated with low levels of physical activity (42, 43), higher concentrations of circulating estradiol (44), as well as increased endometrial cancer risk (45). Moreover physical activity, has been associated with increased adiponectin levels independently of body weight changes (113).

## **5.4 PUBLIC HEALTH IMPORTANCE**

Given the continuously increasing prevalence of obesity, diabetes and physical inactivity in Western societies these 3 studies have important public health implications in term of endometrial cancer prevention. With each year a great and continuously growing percentage of the population is at increased risk for endometrial cancer. The observation that being obese and having low physical activity further increases risk for endometrial cancer in diabetic women provides new opportunities to prevent endometrial carcinogenesis. Preventive strategies can focus on diabetic individuals by promoting risk reduction such as reducing body weight and increasing physical activity. These observations, if confirmed, are of important clinical significance not only in the prevention of endometrial cancer, but also potentially in the management of diabetic subjects, especially those with obesity and low physical activity levels. Our results support the importance of physical activity in the etiology of endometrial cancer and if confirmed these data may prove to be of major public health significance given the increasing prevalence of physical inactivity in Western societies.

Interventions to reduce body weight, increase physical activity and limit inactivity may have important health implications in terms of prevention of endometrial cancer, and future management of diabetic subjects.

## **5.5 FUTURE RESEARCH**

Physical inactivity, obesity and diabetes can all be viewed as a continuum from mild hyperinsulinemia to severe. Future detailed studies to elucidate how much each factor contributes to the observed risk and of the mechanisms underlying the association can give us greater understanding of the mechanisms leading to cancer and could also provide novel therapeutic opportunities.

Based on the results from the meta-analysis on diabetes and endometrial cancer risk, which strongly supports an association between diabetes and endometrial cancer development but due to limited data not an association with endometrial cancer mortality, future studies should focus on diabetes as a factor influencing mortality.

It is widely known and accepted that physical activity is associated with health. But several areas need further investigation, the relation of physical activity in carcinogenesis and cancer survival, are two examples of areas in great need of further development. The study on physical activity and endometrial cancer risk clearly suggest the importance of physical activity, but which type of activity or intensity and which time period of life that is of most importance is still quit unclear. Since the only suitable method to assess physical activity in a large scale epidemiologic study is questionnaire based, these issues must be taken under careful consideration when designing the questionnaire. Our study is the first to study leisure time inactivity directly and we suggest that this is an important factor overlooked by previous studies. It is also a variable were we got very good validity which indicate that it might be easier to get good quality data on inactivity than on activity.

## 6 CONCLUSION

- Diabetes is associated with a nearly 2-fold increased risk for endometrial cancer development in the Swedish Mammography Cohort.
- The association between diabetes and endometrial cancer seems to be more pronounced when diabetic women are obese and not physically active.
- Result from the meta-analysis strongly supports an association between diabetes and endometrial cancer development (2-fold increase), but does not support an association between diabetes and endometrial cancer mortality.
- Total physical activity is weakly inversely associated with endometrial cancer risk in the Swedish Mammography Cohort.
- Five hours a day or more spent on physical inactivity during leisure time, like watching TV or sitting, is statistically significantly associated with a 66% increased risk for endometrial cancer in the Swedish Mammography cohort.

## **7 SAMMANFATTNING (SUMMARY IN SWEDISH)**

### **7.1 SYFTE**

Mer och mer pekar på att hyperinsulinemi i sammanhanget insulinresistens är associerat till uppkomst av cancer. Epidemiologiska studier har observerat en ökad risk av livmodercancer i relation till höga nivåer av C-peptider vilket är en indikation på hyperinsulinemi och låga nivåer av adiponektin (endogent ämne som ökar känsligheten för insulin). Fysisk aktivitet är involverad i regleringen av metaboliska och hormonella system och är en viktig faktor för att bibehålla kroppsvikten; fetma har visats vara en riskfaktor för livmodercancer. En koppling mellan fysisk aktivitet och livmodercancer genom hormonella mekanismer eventuellt genom kroppsvikt är biologisk troligt. De främsta föränderliga determinanterna av insulinresistens, hyperinsulinemi och diabetes så som fetma och fysisk aktivitet, har också visat sig vara riskfaktorer för livmodercancer. Inga tidigare studier har undersökt om fysisk inaktivitet, en viktig determinant för insulin resistens, förändrar sambandet mellan diabetes och livmodercancerrisk. Inga tidigare studier har utvärderat den kombinerade effekten av diabetes, fetma och fysisk inaktivitet som en riskfaktor för livmodercancer. Ingen tidigare metaanalys av diabetes och livmodercancerrisk har gjorts. Inte heller fanns det någon tidigare studie som hade undersökt effekten av fysisk inaktivitet på fritiden.

### **7.2 DESIGN OCH METOD**

I den första studien undersökte vi sambandet mellan diabetes och uppkomst av livmodercancer och den potentiella effektmodifikationen av fetma och fysisk aktivitet i den Svenska Mammografikohorten, en populationsbaserad prospektiv kohort bestående av 36 773 kvinnor. Under en medeluppföljningstid av 7 år mellan 1997 och 2005 diagnostiserades 225 nya livmodercancerfall (adenocarcinoma). I analyserna kontrollerade vi för ålder, BMI och total fysisk aktivitet.

I metaanalysen identifierade vi studier genom litteratursökningar på Pub-Med fram till och med den 31 augusti, 2006, och genom att leta igenom referenslistor i relevanta artiklar. Summerade relativa risker med 95% konfidensintervall räknades ut med en slump-effekts-modell.

I den tredje studien undersökte vi sambandet mellan total fysisk aktivitet och olika typer av fysisk aktivitet med livmodercancerrisk i den Svenska Mammografikohorten innehållandes 33 723 kvinnor och 199 livmodercancerfall efter utslutningar på grund av saknade värden för enskilda frågor om olika typer av fysisk aktivitet. I analyserna kontrollerade vi för faktorer som kunde påverka sambandet så som ålder, BMI, paritet, diabetes, totalt intag av frukt och grönsaker och utbildning.

### **7.3 RESULTAT**

#### **7.3.1 Artikel I**

Efter justeringar för ålder, BMI och total fysisk aktivitet blev den relativa risken för livmodercancer bland kvinnor, med diabetes jämfört med kvinnor utan diabetes 1.94, 95% CI = 1.23 till 3.08. Bland diabetiker med fetma var RR = 6.39, 95% CI = 3.28 till 12.06, jämfört med kvinnor utan fetma och diabetes. Bland diabetiker med låg fysisk aktivitet var RR för livmodercancer 2.80, 95% CI = 1.62 till 4.85, jämfört med fysiskt aktiva kvinnor utan diabetes. Slutligen, feta diabetiker med en låg nivå av fysisk

aktivitet hade en RR= 9.61, 95% CI=4.66 till 19.83, jämfört med kvinnor utan fetma och diabetes med en hög fysisk aktivitetsnivå.

### **7.3.2 Artikel II**

Analys av 16 studier (3 kohorter och 13 fall-kontrollstudier) innehållandes 96 003 deltagare och 7596 livmodercancerfall fann att diabetes var statistiskt signifikant associerat med en ökad risk för livmodercancerincidens, (summerat RR = 2.10 95% CI= 1.75-2.53). Effektestimaten var något starkare bland fall-kontrollstudier (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 multivariat 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 livmodercancermortalitet.

### **7.3.3 Artikel III**

Relativ risk för livmodercancer för den andra till fjärde kvartilen av total fysisk aktivitet jämfört med den lägsta var 0.80 (95% CI 0.54-1.18); 0.87 (95% CI 0.59-1.28); 0.79 (95% CI 0.53-1.17). En hög nivå av inaktivitet på fritiden (se på TV/sitta ner 5 timmar eller mer per dag) jämfört med en låg nivå var associerat med en ökad risk för livmodercancer RR=1.66 (95% CI 1.05-2.61). Sambandet förändrades inte över BMI.

## **7.4 SLUTSATS**

Vi observerade en statistisk signifikant samband mellan diabetes och livmodercancer i vår kohort. Vi observerade ett ännu starkare samband bland feta och inaktiva individer. Resultat från metaanalysen (som inkluderar våra tidigare resultat) stödjer starkt en relation mellan diabetes och ökad risk för livmodercancerincidens. Punktestimaterna från våra kohortanalyser och metaanalysen är mycket lika och pekar på en dubbelt så hög risk för livmodercancer bland diabetiker.

Våra resultat i studien av sambandet mellan fysisk aktivitet och livmodercancer pekar på att total fysisk aktivitet är svagt associerat med livmodercancerrisk och att inaktivitet på fritiden är statistiskt signifikant associerat med en ökad risk för livmodercancer.

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