Diabetes and Risk of Endometrial Cancer: A Population-Based Prospective Cohort Study

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Abstract

Although there is accumulating evidence that hyperinsulinemia in the context of insulin resistance is associated with carcinogenesis, only one prospective study of endometrial cancer incidence, in relation to diabetes, addressed this issue and showed no significant positive association. No previous study has investigated whether physical activity can modify the association between diabetes and endometrial cancer. We examined the association between diabetes and incidence of endometrial cancer and the potential effect modification by obesity and physical activity in the Swedish Mammography Cohort, a prospective cohort of 36,773 women, including 225 incident endometrial adenocarcinoma cases. After adjustments, the relative risk (RR) for endometrial cancer among women with diabetes comparing with nondiabetic women was 1.94 [95% confidence interval (95% CI), 1.23-3.08]. Among obese diabetics, the RR was 6.39 (95% CI, 3.28-12.06) compared with nonobese nondiabetic women. Among diabetics with low physical activity, the RR for endometrial cancer was 2.80 (95% CI, 1.62-4.85) compared with physically active nondiabetic women. Obese diabetics with low physical activity had a RR of 9.61 (95% CI, 4.66-19.83) compared with normal weight nondiabetic women with high physical activity. Diabetes was associated with a 2-fold increased risk, and combination of diabetes with obesity and low physical activity was associated with a further increased risk for endometrial cancer. Interventions to reduce body weight and increase physical activity may have important implications in terms of prevention of endometrial cancer and future management of diabetic subjects. (Cancer Epidemiol Biomarkers Prev 2007;16(2):276–80)

Introduction

There is accumulating evidence that hyperinsulinemia, in the context of insulin resistance, is associated with carcinogenesis (1) and that hyperinsulinemia and insulin resistance are associated with a more aggressive course of endometrial cancer (2). In addition, epidemiologic studies have observed an elevated risk of endometrial cancer in relation to both high prediagnostic C-peptide concentrations indicating hyperinsulinemia (3) and low adiponectin concentrations (a novel endogenous insulin sensitizer; ref. 4). Moreover, long-term insulin therapy of patients with type 1 diabetes may also be responsible for increased risk of endometrial cancer in diabetic women with type 1 diabetes (5).

The major modifiable determinants of insulin resistance, hyperinsulinemia, and diabetes, such as obesity (6, 7) and physical inactivity (8), have also been shown to be risk factors for endometrial cancer (9, 10). Although several studies have reported a positive association between diabetes and incidence of or mortality from endometrial cancer, no previous study has investigated whether physical inactivity, an important determinant of insulin resistance, is a modifier of the association between diabetes and risk of endometrial cancer. Furthermore, no previous study has evaluated a combined effect of diabetes, obesity, and physical inactivity as a predictor of endometrial cancer risk. Besides, several previous studies were limited by small sample size (11-16) and/or an inability to account for important covariates (5, 11-13, 15, 17-21). Only two prospective cohort studies (22, 23) and four case-control studies (24-27) were adjusted for potential confounders. The two cohort studies have shown statistically nonsignificant positive associations between diabetes and incidence of (22) or mortality from (23) endometrial cancer, and the case-control studies have shown significant positive associations with incidence of endometrial cancer. Furthermore, only one prospective cohort (22) and three case-control studies (14, 25, 26) have reported on diabetes in relation to endometrial cancer risk in subgroups of women defined by body mass index (BMI) but none of them took into account physical activity.

To address these unanswered questions, we used data from the Swedish Mammography Cohort, a population-based prospective cohort study of ~40,000 women. We examined associations between diabetes and endometrial cancer risk and investigated whether the association varied by body weight and/or level of total physical activity, two major determinants of insulin resistance/hyperinsulinemia as well as risk factors for endometrial cancer, after adjusting for other known risk factors. Furthermore, we examined association between diabetes combined with obesity and/or physical inactivity and endometrial cancer risk.

Materials and Methods

From 1987 to 1990, all women who lived in the Uppsala County of central Sweden and were born in 1914 to 1948 (n = 48,517) and all women who lived in the adjacent Västmanland County (n = 41,786) and were born in 1917 to 1948 received an invitation by mail to participate in a mammography screening program. A total of 66,651 (74%) women returned a completed questionnaire on diet, weight, height, parity, and education.

We excluded 5,188 women due to incorrect or missing identification numbers, dates missing on the questionnaire, moving out of the study area, death, outside the age range 40

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to 76 years, extreme energy intake, or having had a cancer diagnosis.

In 1997, a second questionnaire was sent to all 56,030 members of the cohort who were still living in the study area; the second questionnaire was extended with information on medical history, including diabetes, history of oral contraceptive use, age at menopause, postmenopausal hormone use, and lifestyle factors, such as history of cigarette smoking, use of dietary supplements, and total physical activity; 39,227 (70%) women returned a completed questionnaire. Of the 39,227 women who responded to the 1997 questionnaire, we excluded those diagnosed with cancer (other than nonmelanoma skin cancer; $n = 1,981$) and those having had a hysterectomy ($n = 473$) before returning the questionnaire. After these exclusions, 36,773 women ages 50 to 83 years remained for this analysis.

Diabetes was self-reported on the questionnaire and assessed with a question ''have you ever been diagnosed with diabetes'' (e.g., outpatient, n = 1,509) and obtained by computerized linkage of the study population with the Swedish In-patient Registry (n = 675). BMI was calculated as weight in kilogram divided with the square of the length in meters (kg/m^2). The validity for self-reported weight and height compared with measurements in Swedish women is high [Pearson correlation coefficient = 0.9 and 1.0, respectively (28)]. Estimated total physical activity was based on five types of activities, such as home/household work, walking/cycling, work/occupation, TV/reading, and exercise, and measured as multiples of the metabolic equivalent (MET, $kcal \cdot kg^{-1} \cdot h^{-1}$). The physical activity questions were validated by comparing with two 1-week records; Spearman correlation coefficient was 0.7 (29). 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. Energy intake was assessed with the use of a self-administered food-frequency questionnaire that included food items (including alcoholic beverages) commonly consumed in Sweden. We used age-specific (<53, 53-65, and >65 years) portion sizes that were based on mean values obtained from 213 randomly chosen women from the study area who weighed and recorded their foods during four 1-week periods 3 to 4 months apart.[3]

Follow-up of the Cohort. 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. The Swedish Cancer Registry and the Regional Cancer Registry have been estimated to be ~100% complete (30).

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.

This study was approved by the Ethics Committees at the Uppsala University Hospital (Uppsala, Sweden) and the Karolinska Institutet (Stockholm, Sweden). Completion of the self-administered questionnaire indicated informed consent to participate in this study.

Statistical Analysis. To estimate the risk of endometrial cancer, we used Cox proportional hazards regression models. 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 June 30, 2003 to June 30, 2005 (because for this time, we only have regional information), or the end of follow-up (June 30, 2005), whichever came first. The relative risk (RR) of endometrial cancer [with 95% confidence interval (95% CI)] was calculated by dividing the incidence rate among diabetic women with that among nondiabetic women. We did age-adjusted (age in months) and multivariable analyses. The multivariable models simultaneously included such variables as BMI and total physical activity, which changed risk estimates of diabetes by ≥5%. We also did multivariable analysis further adjusted for known risk factors, such as use of postmenopausal hormones, oral contraceptive use, parity, age at menopause, education, smoking, and total energy intake.

We conducted analyses of diabetes stratifying by BMI and physical activity. We also did analysis examining the joint effect of diabetes combined with obesity and diabetes combined with low physical activity (inactivity). Furthermore, we evaluated the joint effect of diabetes combined with obesity and low physical activity. The statistical significance of interactions was tested by adding an interaction term to the Cox model, simultaneously containing the main variables and age in months. All analyses were done using Statistical Analysis System software version 9.1 (SAS Institute, Cary, NC).

Results

During a mean follow-up of 36,773 women in the cohort for 7 years (265,648 person-years), 225 endometrial cancer cases were diagnosed. The mean age at diagnosis of endometrial cancer was 68.6 (±9.5) years. Table 1 shows the distribution of known and potential risk factors for endometrial cancer in diabetic and nondiabetic subjects of the cohort. Individuals diagnosed with diabetes were older and heavier than nondiabetics, had a little lower total physical activity and less education, and tended to have used less postmenopausal hormone treatment and oral contraceptives. Other characteristics did not differ substantially between diabetics and nondiabetics. Overall diabetes was positively associated with endometrial cancer risk in both age-adjusted and multivariate analyses adjusting for confounders, such as BMI and total physical activity. The multivariate RR of endometrial cancer was 1.94 (95% CI, 1.23-3.08) for women diagnosed with diabetes compared with women without diabetes (Table 2). Adjusting for BMI as a categorical (quartiles) variable compared with as a continuous did not change the risk estimate (RR, 1.93; 95% CI, 1.22-3.06). Additional adjustment for potential confounders, such as use of postmenopausal hormones, oral contraceptive use, parity, age at menopause, education, smoking, and total energy intake, did not change

Table 1. Baseline characteristics of women according to diabetes diagnosis

Variables	Diabetes	
	No (n = 35,145)	Yes (n = 1,628)
Age (y)	61.7	66.5
BMI (kg/m^2)	24.9	27.5
Total physical activity (MET/h)	42.5	42.0
No. children	2.1	2.2
Oral contraceptive use (%)	58.4	51.0
Age at menopause (y)	49.9	49.7
Postmenopausal hormone use (%)	51.7	44.7
Total energy intake (kcal/d)	1,725	1,755
Education ≥12 y (%)	16.1	12.1
Never smokers (%)	52.9	51.4
Current smokers (%)	19.7	19.5

NOTE: All values other than for age have been directly standardized according to the age distribution of the cohort.

[3] A. Wolk, unpublished data.

Table 2. Association of diabetes with the risk of endometrial cancer

	No diabetes, RR (95% CI)	Diabetes, RR (95% CI)
No. cases	203	22
Person-years	254,760	10,887
Adjusted for age*	1.0 (reference)	2.37 (1.51-3.74)
Adjusted for age and BMI †	1.0 (reference)	1.97 (1.24-3.11)
Adjusted for age and physical activity ‡	1.0 (reference)	2.33 (1.48-3.68)
Adjusted for age, physical activity, and BMI§	1.0 (reference)	1.94 (1.23-3.08)

*Adjusted for age (in months).
†Adjusted for age (in months) and BMI (kg/m^2, continuous).
‡Adjusted for age (in months) and total physical activity (MET/h quartiles <38.8, 38.9-42.1, 42.2-45.8, 45.9+).
§Adjusted for age (in months), BMI (kg/m^2, continuous), and total physical activity (MET/h quartiles <38.8, 38.9-42.1, 42.2-45.8, 45.9+).

the results substantially (RR, 1.96; 95% CI, 1.23-3.12). In sensitivity analysis, after exclusion of women with missing values of any single covariable included in the additionally adjusted multivariable model, the result did not differ substantially from the original analyses (RR, 1.98; 95% CI, 1.11-3.53). To eliminate potential effects of early undiagnosed endometrial cancer, we repeated our analysis after excluding endometrial cancer cases diagnosed during the first year of follow-up. Results from this analysis did not differ substantially from those for the whole cohort (multivariable RR, 1.77; 95% CI, 1.06-2.97, including 193 cases).

In an attempt to better disentangle the association of diabetes from the association of obesity and physical inactivity with the increased risk of endometrial cancer, we did analyses stratified by BMI and physical activity (Table 3). Because there were small differences in mean BMI between diabetics and nondiabetics within the two BMI strata (diabetics had on average slightly higher BMI), we adjusted for BMI within BMI strata. We observed an ~3-fold increased risk for obese women with diabetes comparing with obese women without diabetes. Similarly, women classified as having low physical activity had an ~3-fold increased risk if they had diabetes.

We also evaluated the joint effect of diabetes combined with obesity and diabetes combined with low physical activity on the risk of endometrial cancer (Table 4). In stratified analysis, using as reference group nondiabetic women with low BMI, women with diabetes and high BMI had a >6-fold increased risk. However, a formal test did not show a statistically significant interaction between diabetes and BMI ($P_{interaction}$ = 0.25). When stratifying on total physical activity, the excess risk for endometrial cancer associated with diabetes and low physical activity was statistically significantly 3-fold higher compared with nondiabetic women with high physical activity. There was a statistically significant interaction between physical activity and diabetes ($P_{interaction}$ = 0.002). Further, we examined the joint effect of diabetes combined with high BMI and physical inactivity in relation to endometrial cancer risk, dividing the subjects according to the same cutoff points as in the above analyses in Table 4. Obese, physically inactive, diabetic women (including 9 endometrial cancer cases) had a RR of 9.61 (95% CI, 4.66-19.83) in age-adjusted analysis when compared with nondiabetic, nonobese women with high physical activity (including 75 endometrial cancer cases).

Discussion

In this population-based prospective cohort study, women with diabetes had a statistically significant ~2-fold higher risk for developing endometrial cancer. The risk was increased >6-fold among obese diabetic women compared with normal weight women without diabetes, whereas diabetics with low level of physical activity had ~3-fold increased risk compared with women without diabetes and a high level of total physical activity. In contrast, physically active diabetic women did not have significantly increased risk for endometrial cancer compared with women without diabetes; however, this observation was based on a very few cases. Subjects with the most unfavorable combination of diabetes with both high BMI and low physical activity had ~10-fold higher risk in comparison with nondiabetic women with normal weight who were highly physically active.

This is the first prospective cohort study showing diabetes to be statistically significantly associated with incidence of endometrial cancer and agrees and extends findings from case-control studies (14, 24-27). Two previous cohort studies suggested a positive overall association of diabetes with endometrial cancer incidence (multivariate RR, 1.43; 95% CI, 0.98-2.1; ref. 22) as well as mortality (multivariate RR, 1.33; 95% CI, 0.92-1.90; ref. 23), but results did not achieve statistical significance. Our observation that the risk is higher among obese diabetic women than among obese nondiabetic women is in accordance with the results from the previous case-control studies (14, 25, 26) and one cohort study (22). Furthermore, we have shown that the association between diabetes and endometrial cancer may be significantly modified by physical activity. Physically active diabetics were not at increased risk for endometrial cancer. 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. Given the pandemic of obesity and the increasing prevalence of diabetes and physical inactivity in

Table 3. Association of diabetes with risk of endometrial cancer stratified by BMI and physical activity

		Mean BMI	No. cases	Person-years	RR (95% CI)
BMI (kg/m^2)*					
<30	No diabetes	24.04	154	229,793	1.0 (reference)
	Diabetes	25.11	11	8,237	1.55 (0.83-2.91)
≥30	No diabetes	32.93	43	24,968	1.0 (reference)
	Diabetes	33.66	11	2,650	2.65 (1.37-5.15)
Physical activity (MET/h) †					
High ‡	No diabetes	24.75	103	141,369	1.0 (reference)
	Diabetes	27.52	5	4,905	1.06 (0.43-2.60)
Low§	No diabetes	25.15	100	113,392	1.0 (reference)
	Diabetes	27.51	17	5,981	2.67 (1.58-4.53)

*Adjusted for age (in months), total physical activity (MET/h quartiles <38.8, 38.9-42.1, 42.2-45.8, 45.9+), and BMI (kg/m^2, continuous).
†Adjusted for age (in months) and BMI (kg/m^2, continuous).
‡The highest and middle tertiles of total physical activity combined.
§The lowest tertile of total physical activity (<39.8 MET/h).

Table 4. Association of diabetes combined with obesity and of diabetes combined with low physical activity (inactivity) with risk of endometrial cancer

	No diabetes		Diabetes		*P* for interaction
	No. cases	RR (95% CI)	No. cases	RR (95% CI)	
BMI (kg/m^2)*					
<30	154	1.0 (reference)	11	1.75 (0.93-3.30)	
≥30	43	2.49 (1.77-3.51)	11	6.39 (3.38-12.06)	0.25
Physical activity (MET/h)†					
High‡	103	1.0 (reference)	5	1.12 (0.45-2.75)	
Low§	100	1.09 (0.82-1.45)	17	2.80 (1.62-4.85)	0.002

*Adjusted for age (in months) and total physical activity (MET/h quartiles <38.8, 38.9-42.1, 42.2-45.8, 45.9+).
†Adjusted for age (in months) and BMI (kg/m^2, continuous).
‡The highest and middle tertiles of total physical activity combined.
§The lowest tertile of total physical activity (<39.8 MET/h).

Western societies, these findings have also important public health implications, suggesting that a great and continuously growing percentage of the female population is at increased risk for endometrial cancer.

There are several mechanisms that could be potentially involved in the development of endometrial cancer in diabetic women. Hyperinsulinemia is a hallmark of diabetes, obesity, and physical inactivity, and insulin has been shown to stimulate the growth of endometrial stromal cells by binding to insulin receptors on endometrial cells (31). Hyperinsulinemia may also increase levels of free estrogens through decreasing concentrations of circulating sex hormone–binding globulin (32, 33). Estrogens have in turn been shown to increase endometrial cancer risk by stimulating proliferation of endometrial cells (34) when unopposed by progesterone (especially in postmenopausal women; refs. 35, 36). Finally, hyperinsulinemia through decreasing levels of insulin-like growth factor (IGF)-binding protein-1 and IGF-binding protein-3 increases circulating free IGF-I, which by binding and activating IGF-I receptors in the endometrium stimulates cell proliferation (37-42). Decreased circulating IGF-binding protein-3 levels may also have a direct regulatory role in cell growth control and cancer (43, 44). We have recently reported that obesity is closely associated with lower circulating levels of an endogenous insulin sensitizer, adiponectin (45), which in turn leads to type 2 diabetes and hyperinsulinemia. Low adiponectin levels are not only associated with higher levels of circulating estradiol and hyperinsulinemia/insulin resistance (46) but may also directly alter cell proliferation/apoptosis and angiogenesis by a process that involves members of the caspase group of apoptotic enzymes (47).

Thus, the higher risk observed among diabetic women could be due to their reduced adiponectin levels as well as increased insulin and IGF-I levels. The even higher risk observed in obese diabetic women is compatible with the fact that obesity induces both a state of significant hypoadiponectinemia and hyperinsulinemia as well as an excess of circulating bioactive endogenous estrogens due to an increased estrogen production from aromatization of androgens in peripheral fat tissue (48-50) and/or through a decreased production of sex hormone–binding globulin (51). In this respect, it is interesting to note that we have recently observed that reduced adiponectin levels are associated with increased risk for endometrial cancer and a combination of obesity with reduced adiponectin levels increases risk even further (i.e., 6-fold; ref. 52).

The lack of increased risk observed among physically active diabetics observed in our study may reflect the increased insulin sensitivity found in physically active women (53) and/or a shift in body composition containing less body fat and visceral adipose tissue (6, 7). The latter has been associated with higher adiponectin levels and lower degree of insulin resistance/hyperinsulinemia (54). Future detailed studies of the mechanisms underlying these epidemiologic observations can elucidate further the mechanisms leading to endometrial cancer and could also provide novel therapeutic opportunities. This study has important public health implications in terms of endometrial cancer prevention, given the continuously increasing prevalence of obesity and diabetes mainly due to inactivity and unhealthy diets, in Western societies. The observation that being obese and having low physical activity is further increasing risk for endometrial cancer in diabetic women provides new opportunities to prevent endometrial carcinogenesis in diabetic subjects by focusing on modifiable predictors of risk, such as body weight reduction and physical activity.

Major strengths of our study include its population-based design and the completeness of identification of endometrial cancer cases through the Swedish cancer registries. The prospective nature of the study fulfills the time sequence criterion for causality and makes it highly unlikely that the associations we observed were due to recall or selection biases, which can lead to spurious associations in case-control studies. Furthermore, we had information on all major potential confounders.

One limitation of our study is that identification of diabetic women in the cohort was partly based on self-reports, which might lead to underestimation of the true prevalence of diabetes. Incomplete identification of diabetic women in the cohort could lead to attenuation of our results. 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. Furthermore, we had no information on duration of diabetes or treatment given. We could adjust only for BMI, and we were unable to control for body fat distribution, which would be more appropriate. Although the possibility of uncontrolled or residual confounding cannot be entirely eliminated, we have adjusted for multiple potential confounders. Another limitation is that it is difficult to clearly disentangle the association of diabetes from the association of obesity and physical inactivity with increased risk of endometrial cancer. Obesity and physical inactivity are two important risk factors for diabetes and also for endometrial cancer. Physical inactivity, obesity, and diabetes are associated with different degrees of hyperinsulinemia. Diabetes could therefore be an intermediate factor in the etiology of endometrial cancer.

In conclusion, our results suggest that diabetes may increase risk for endometrial cancer especially when combined with obesity and/or physical inactivity. If confirmed by other studies and in other populations, these data may prove of major public health significance given the increasing prevalence of obesity, physical inactivity, and diabetes in Western societies. Interventions to reduce body weight and increase physical activity may have important implications in terms of prevention of endometrial cancer and future management of diabetic subjects.

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