Diabetes and Endometrial Cancer in the Iowa Women's Health Study[1]

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Abstract

Diabetes has been associated with increased risk of endometrial cancer in some epidemiological studies. Body mass index (BMI) and other measures of obesity have been associated positively with both diabetes and endometrial cancer. It is not clear whether or not the association of diabetes with endometrial cancer is explained entirely by obesity. Thus, we sought to test the hypothesis that diabetes is not associated with endometrial cancer independent of obesity. We examined the association between self-reported diabetes (onset at >30 years of age) and incident endometrial cancer in a prospective cohort study of 24,664 postmenopausal women in Iowa. Over 12 years of follow-up, 346 cases occurred among the cohort at risk. Data were analyzed using proportional hazards regression models. Diabetes was analyzed as reported at baseline and as a time-dependent variable using information obtained during follow-up. After adjustment for BMI, waist:hip ratio, and other covariates, the relative risk (RR) for women with diabetes *versus* women without diabetes was 1.43 [95% confidence interval (CI), 0.98–2.1]. The diabetes association was confined to women in the upper two BMI quintiles (RR, 1.47; 95% CI, 0.98–2.20), but a formal test of interaction was not statistically significant. Analyses that included diabetes ascertained at baseline and at follow-up gave similar results; the diabetes-associated RR in the higher BMI strata was 1.64 (95% CI, 1.16–2.31). We conclude that after adjustment for other risk factors, diabetes is associated with a modestly increased risk for endometrial cancer among women in this cohort.

Introduction

Endometrial cancer is the fourth leading incident cancer in women in the United States (1). Incidence peaks between the ages of 70 and 74 years, and with an aging United States population, an increasing number of women will be diagnosed with this disease.

Epidemiological studies indicate that estrogens, both endogenous and exogenous, have a major role in endometrial carcinogenesis (2–4). Obesity, as measured by an elevated BMI,[4] is also a consistent risk factor for endometrial cancer (2). Various measures of fat distribution, such as WHR, have been reported to be associated with increased risk of endometrial cancer, although less consistently than BMI (5–7).

Obese women have higher levels of estradiol, non-protein-bound estradiol, and estrone than do women of normal weight (8), and this has been considered to be the major reason for the excess risk of endometrial cancer due to obesity (9). However, some researchers have argued that elevated estrogen levels in obese women are not sufficient to explain the excess risk due to obesity and that other factors, such as the higher insulin levels that occur in obese women, may increase risk for endometrial cancer (10, 11). Given that insulin can increase the levels of sex hormones and growth factors and has direct mitogenic effects on endometrial tissue, this argument is plausible (12–16).

Type 2 (adult-onset) diabetes has been associated positively with endometrial cancer occurrence in some but not all epidemiological studies (2). Because diabetes is associated positively with obesity (17), the apparent increased risk of endometrial cancer in diabetic women may reflect this shared risk (3, 4, 7, 17).

Cohort studies have reported both positive (18–21) and negative associations with endometrial cancer (22), but these studies did not fully adjust for confounders. Case-control studies have generally reported positive associations between diabetes and endometrial cancer (2, 4, 23–30), but again, not all studies adjusted for potential confounders. Thus, it is not clear what role, if any, diabetes plays in the etiology of endometrial cancer.

Previous analysis from the IWHS showed that WHR is not associated with endometrial cancer after adjustment for BMI (7). Here, we analyzed data from the Iowa cohort to test our hypothesis that type 2 diabetes and endometrial cancer are not associated after adjustment for BMI.

Materials and Methods

The IWHS is a prospective cohort study designed to explore the association of body fat distribution with incident cancers in postmenopausal women (31). Briefly, in January 1986, a

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[4] The abbreviations used are: BMI, body mass index; WHR, waist:hip ratio; HRT, hormone replacement therapy; IWHS, Iowa Women's Health Study; OC, oral contraceptive; RR, relative risk; CI, confidence interval; SHBG, sex hormone-binding globulin; IGFBP-3, insulin-like growth factor-binding protein 3; IGF-I, insulin-like growth factor.

random sample of 98,826 women (age, 55–69 years) in Iowa were sent questionnaires. The women were selected from the 1985 Iowa driver's license list; 41,836 women (43%) returned questionnaires and comprise the study cohort. Identifying information was available on nonrespondents (the driver's license number is the social security number). Respondents and nonrespondents had similar demographic measures and rates of endometrial cancer (32).

The baseline self-administered questionnaire collected information on potential risk factors for endometrial cancer, including education; ages at menarche, menopause, and first live birth; number of pregnancies, miscarriages, and abortions; exogenous hormone use; medical history; family history of cancers; physical activity; height; and weight history. Prevalent diabetes mellitus was ascertained by the following question: "Have you ever been told by a doctor that you have sugar diabetes (diabetes mellitus)?" Age at diagnosis was also requested. Incident diabetes was ascertained at each of the follow-up surveys in 1987, 1989, 1992, and 1997. Subjects diagnosed at <30 years of age were excluded from these analyses to limit this study to women with probable type 2 diabetes (33). Participants were also asked if they had ever taken insulin or "pills for sugar diabetes (or to lower blood sugar)."

HRT use was determined from the following question: "Have you ever used pills other than birth control pills which contain estrogen or other female hormones (for example, at the change of life or menopause, after surgery, or at any other time)?"

Weight and height measurements were requested, and BMI was calculated as weight (kg)/height (m^2). Also included with the questionnaire was a paper tape measure. Study subjects were asked to enlist assistance to measure the following circumferences: (*a*) waist (measured 1 inch above the umbilicus); and (*b*) hips (maximal protrusion). These measurements were used to compute the WHR. Measurements obtained by this protocol are shown to be reliable and accurate (34).

Periodic mail surveys identified emigrants from Iowa and deaths. For cohort members within Iowa, cancer incidence and mortality verification were ascertained by linkage to the State Health Registry of Iowa, part of the National Cancer Institute's Surveillance, Epidemiology, and End Results Program. Deaths outside of Iowa and among follow-up survey nonresponders were verified through linkage with the National Death Index of the National Center for Health Statistics.

Data Analysis. Participants were excluded from analysis if they reported any of the following at baseline: (*a*) a hysterectomy ($n = 14,350$); (*b*) premenopausal status ($n = 569$); (*c*) history of cancer other than non-melanoma skin cancer ($n = 3830$); or (*d*) diabetes diagnosed before the age of 30 years ($n = 266$). Some women had more than one exclusion characteristic. After these exclusions, 24,664 women remained in the cohort. Women were considered to be at risk from the date of the baseline questionnaire completion through December 31, 1997 or earlier, on the occurrence of one of the following events: (*a*) emigration from Iowa (outmigration is less than 1% per year); (*b*) endometrial cancer diagnosis; or (*c*) death. Women diagnosed with adenocarcinoma, adenoacanthoma, or adenosquamous carcinoma of the endometrium were included as cases in these analyses. A total of 346 cases of incident endometrial cancer occurred over 12 years of follow-up.

We compared mean values or prevalences of baseline variables in endometrial cancer cases *versus* noncases and among nondiabetics, insulin-using diabetics, and non-insulin-using diabetics using Student's *t* tests and χ^2 tests, respectively.

Table 1 Mean values (or percentages) of selected baseline characteristics of women who did and did not develop endometrial cancer: IWHS, 1986

Variable	Incident endometrial cancer	
	Yes ($n = 346$) % or mean	No ($n = 24,318$) % or mean
Anthropometric		
Current weight, mean (lbs)	171.5	151.6
Maximum weight, mean (lbs)	182.6	162.4
Current BMI, mean kg/m^2	30.5	26.8
WHR, mean	0.86	0.84
Reproductive		
Nulligravidity (%)	12.7	9.1
OC use (% ever)	14.2	18.7
HRT		
Former use (%)	25.3	21.6
Current use (%)	14.3	4.6
Ovulatory span, mean (yrs)	36.0	34.4
Menstrual irregularity (% ever)	15.4	9.0
Fertility problems (% ever)	14.5	15.5
Miscarriages		
1 (%)	14.0	18.7
>1 (%)	5.0	7.4
Induced abortion (% ever)	2.6	1.6
Medical conditions		
Hypertension (% ever)	45.4	35.1
Diabetes (% ever)	10.0	5.4
Insulin	2.3	1.5
Oral hypoglycemic medications	4.6	2.2
Personal characteristics		
Age, mean (yrs)	62.6	61.8
Physical activity (% low)	50.6	47.1
Education (% ≤ high school graduate)	61.3	60.2

To examine the association of diabetes with incident endometrial cancer, we computed age-adjusted and multivariate-adjusted RRs and their 95% CIs using proportional hazards regression models (SAS Institute, Cary, NC). BMI was represented in the multivariate regression models as either a continuous variable or in quintiles. BMI (kg/m^2) quintiles were as follows: (a) quintile 1, ≤22.87; (*b*) quintile 2, 22.88–25.01; (*c*) quintile 3, 25.02–27.41; (*d*) quintile 4, 27.42–30.7; and (*e*) quintile 5, ≥30.71. Other covariates from the preliminary analyses were added to the regression models one at a time and in groups to find the best models based on *a priori* decisions or statistical significance of covariates.

We accounted for diabetes diagnosed after baseline by modeling diabetes as a time-dependent variable. For this particular analysis, nonresponders to questionnaires after baseline were considered nondiabetic.

Possible interactions of BMI and diabetes were evaluated formally by comparing the −2 log likelihoods of proportional hazards regression models with and without the cross-product (interaction) term.

Results

Women who developed endometrial cancer had higher mean BMI and WHR values than noncases (Table 1); these findings were consistent with earlier reports from this cohort (3). Baseline mean current and heaviest adult weights also were higher in cases *versus* noncases. Women who developed endometrial cancer were more likely to be nulligravid (12.7% *versus* 9.1%), were less likely to have used birth control pills (14.2% *versus*

Table 2 Mean values (or percentages) of baseline characteristics according to self-reported diabetes status and insulin use: IWHS, 1986

Variable	Diabetes status		
	Yes		No
	Insulin users (n = 360) % or mean	Non-insulin users (n = 965) % or mean	(n = 23,150) % or mean
Anthropometric			
Current weight, mean (lbs)	176.3	171.2	150.6
Maximum weight, mean (lbs)	197.1	193.4	160.7
Current BMI, mean (kg/m^2)	31.3	30.5	26.6
WHR, mean	0.91	0.90	0.83
Reproductive			
Nulligravidity (%)	9.5	8.7	9.1
OC use (% ever)	15.0	17.0	18.8
HRT use			
Former use (%)	16.9	21.0	21.7
Current use (%)	2.5	3.5	4.8
Ovulatory span, mean (yrs)	34.3	34.4	34.5
Menstrual irregularity (% ever)	9.9	12.3	8.9
Fertility problems (% ever)	17.6	13.6	15.5
Miscarriages			
1 (%)	23.5	19.5	18.5
>1 (%)	8.9	9.5	7.2
Induced abortion (% ever)	3.4	1.8	1.6
Medical conditions			
Hypertension (% ever)	69.2	65.9	33.3
Personal characteristics			
Age, mean (yrs)	62.6	62.5	61.7
Physical activity (% low)	56.5	56.2	46.5
Education (% ≤ high school graduate)	67.3	69.4	59.6

18.7%), and were more likely to have ever used HRT than noncases. Compared with noncases, incident endometrial cancer cases had longer ovulatory spans and were more likely to have had menstrual irregularities. Women who developed endometrial cancer were 30% and 85% more likely than noncases to have reported hypertension and diabetes at baseline, respectively. Women who developed endometrial cancer were older, on average, than noncases, but differences between the two groups with respect to educational status or level of physical activity were not statistically significant.

Diabetics reported higher values than nondiabetics for current weight, maximum lifetime weight, BMI, WHR, and hypertension (Table 2). Diabetics had a lower prevalence of HRT and OC use than nondiabetics and a higher prevalence of menstrual irregularities. Mean ovulatory span was equivalent in the three groups. Compared with nondiabetic women, diabetic women reported lower levels of education and physical activity.

The age-adjusted RR of endometrial cancer among women reporting baseline diabetes compared with those without diabetes was 2.07 (95% CI, 1.45–2.95; Table 3). When only BMI was added to the regression model (in quintiles), the RR dropped to 1.39 (95% CI, 0.97–2.0). The multivariate-adjusted RRs for endometrial cancer among diabetics *versus* nondiabetics were 1.52 (95% CI, 1.05–2.22) with BMI modeled in quintiles and 1.43 (95% CI, 0.98–2.09) with BMI and BMI-squared both modeled as continuous variables.

The age-adjusted RRs of endometrial cancer across BMI (quintiles) were 1.0 (reference), 1.0, 0.92, 1.7, and 4.1, respectively. Additional adjustment for diabetes did not alter these values markedly; the RRs across BMI quintiles were 1.0 (reference), 1.02, 0.92, 1.6, and 4.0.

We wanted to examine whether or not the association of diabetes with endometrial cancer differed for women with higher BMIs *versus* those with lower BMIs. Women were stratified initially into three BMI categories (quintiles 1–3, quintile 4, and quintile 5), and the association for diabetes was examined within each of these strata. RRs for endometrial cancer associated with diabetes in quintiles 4 and 5 were very similar; therefore, data in these quintiles were combined. Subsequent analyses were conducted with two BMI strata.

In the lower BMI category, the RR of endometrial cancer for diabetes was 0.94 (Table 4). Compared with nondiabetic women with lower BMI, nondiabetics with a higher BMI had a RR of 2.75, whereas diabetics with a higher BMI had a RR of 5.14. The RR associated with diabetes among women with higher BMI was 1.75. However, a formal test of interaction was not statistically significant (-2LL $\chi^2 = 0.73$, $df = 1$; $P > 0.3$).

To examine possible residual confounding in the analyses shown in Table 4, we compared the average BMI among the four groups of women. In the lower BMI category, the mean BMI in those with and without diabetes was not markedly different; however, in the higher category, diabetics had a higher mean BMI than nondiabetics, *i.e.*, 34.0 *versus* 31.6 kg/m^2 ($P < 0.01$). This BMI difference may account for the 75% higher risk of endometrial cancer seen among the diabetics in the higher BMI stratum. In an effort to further reduce possible confounding in the stratified analysis, BMI was added as a continuous variable in the multivariate adjusted model. This further attenuated the RR of diabetes for endometrial cancer in the higher BMI category from 1.75 (95% CI, 1.17–2.61) to 1.47 (95% CI, 0.98–2.2).

We were able to account for diabetes diagnosed after baseline through a time-dependent analysis. An additional 1191 incident cases of diabetes were reported after baseline. Among these women, 37 subsequently developed endometrial cancer (3 of these were women in the lower BMI category). We included diabetes cases ascertained both at and after baseline in a multivariate analysis that, as before, included BMI as a continuous variable. The RRs for endometrial cancer in the low and high BMI categories, respectively, were 1.17 (95% CI, 0.47–2.90) and 1.64 (95% CI, 1.16–2.31).

Discussion

We found a moderately strong positive age-adjusted association between diabetes and endometrial cancer in this cohort of Iowa women. The association was attenuated after adjustment for other endometrial cancer risk factors, particularly BMI. The results were similar when diabetes was modeled as reported at baseline or modeled as a time-dependent variable. Our analyses of the association of diabetes and endometrial cancer, after adjustment for BMI and other risk factors, yielded findings similar to those of other investigators (20, 27, 28).

The results of our stratified analyses are more difficult to compare with those of other investigators. The cut points for "high" and "low" BMI categories differ somewhat from other studies, and we attempted to control for residual confounding of BMI within strata. Based on point estimates, our results are similar to those from a case-control study that indicated that diabetes conferred additional risk of endometrial cancer only on women who were overweight or obese (27). Other studies have found no evidence for effect modification. O'Mara *et al.* (25) and Parazzini *et al.* (29) reported positive associations between diabetes and endometrial cancer across strata of BMI.

Wiederpass *et al.* (20, 28) saw no difference in the effect of diabetes on endometrial cancer when comparing obese

Table 3 Association of diabetes with RR of endometrial cancer: IWHS, 1986–1997

Diabetes	No. of cases[a]	Person-years	RR[b] (95% CI)	RR[c] (95% CI)	RR[d] (95% CI)
No	307	255,933	1.00 (ref)	1.00 (ref)	1.00 (ref)
Yes	34	13,255	2.07 (1.45–2.95)	1.52 (1.05–2.22)	1.43 (0.98–2.09)

[a] Five cases had missing information on diabetes status.
[b] Adjusted for age.
[c] Adjusted for age (years), BMI (quintiles), WHR (quintiles), ovulatory span (years), gravidity (yes, no), HRT use (never, former, current), menstrual irregularities (ever, never), and hypertension (yes, no).
[d] Adjusted for age (years), BMI (continuous), BMI-squared (continuous), WHR (quintiles), ovulatory span (years), gravidity (yes, no), HRT use (never, former, current), menstrual irregularities (ever, never), and hypertension (yes, no).

Table 4 Association of self-reported diabetes (DM) and BMI with risk of endometrial cancer: IWHS, 1986–1997

BMI category[a]	Diabetes	Mean BMI (kg/m^2)	No. of cases	Person-yrs	RR[b] (95% CI)	DM-specific RR[b] (95% CI)	RR[c] (95% CI)	DM-specific RR[c] (95% CI)
Quintiles 1–3	No	23.7	117	160,593	1.0 (ref)		1.0	
	Yes	23.9	3	4,400	0.94 (0.30–2.97)		0.96 (0.30–3.04)	
Quintiles 4 and 5	No	31.6	190	95,341	2.75 (2.11–3.58)	1.00 (ref)	1.52 (1.11–2.09)	1.0 (ref)
	Yes	34.0	31	8,855	5.14 (3.29–8.03)	1.75 (1.17–2.61)	2.36 (1.42–3.90)	1.47 (0.98–2.20)

[a] BMI categories: $\leq$27.41 kg/m^2, quintiles 1–3; and $>$27.41 kg/m^2, quintiles 4 and 5.
[b] Adjusted for age (continuous), WHR (quintiles), ovulatory span (years, continuous), gravidity (ever, never), HRT use status (never, former, current), menstrual irregularities (ever, never), and hypertension (yes, no).
[c] Adjusted for age (continuous), BMI (continuous), WHR (quintiles), ovulatory span (years, continuous), gravidity (ever, never), HRT use status (never, former, current), menstrual irregularities (ever, never), and hypertension (yes, no).

women with nonobese women (BMI $\geq$ 30 kg/m^2 *versus* BMI $<$ 30 kg/m^2 in the latter study). The authors did not present data regarding the diabetes association for women with BMI $<$ 27.4 kg/m^2; therefore, a comparison with our lower BMI category is not possible. However, to an extent, our findings were similar to theirs. We observed an effect of diabetes in women with BMI of 27.41–30.7 kg/m^2 and women with BMI $>$ 30.7 kg/m^2 (quintiles 4 and 5).

Limitations of our study should be considered. A concern in this and many other studies is that as many as 50% of diabetics in the general population are not diagnosed (33). In addition, we assessed diabetes by self-report. Although validation studies suggest that people overreport diabetes compared with physician diagnoses, self-report of this disease appears to have reasonable validity (35, 36). Misclassification of diabetes due to over- or underreporting might alter our results. Biomarkers for diabetes or for intermediate pathways of interest, such as insulin and IGF-I, were not available in this study. In future studies, such measures would facilitate an understanding of these complex associations.

Even in this large study, with an initial sample of over 41,000 women, the number of incident endometrial cancer cases with diabetes was relatively low (n = 34). When these data were stratified into two BMI categories, there were only three endometrial cancer cases among diabetic women in the lower BMI category. The addition of incident diabetics in the time-dependent analysis increased the number of endometrial cancer cases among diabetics to 71 cases overall, 6 of which were in the lower BMI category. Nonetheless, our interpretation regarding the effect of diabetes on the lower BMI subgroup may be limited due to the small number of women in that group.

If we take the view that diabetes and endometrial cancer are not causally related, then the positive association between diabetes and endometrial cancer in this cohort after multivariate adjustment may reflect residual confounding by BMI. This explanation is supported by attenuation of the diabetes association by various means of adjustment for BMI. The fact that adjustment for BMI does not eliminate the association with endometrial cancer may be because the relationship of adiposity to endometrial cancer development is undoubtedly complex (5–7, 37), reflecting the physiological changes that accompany obesity. Thus, even if baseline BMI were measured without error, it may be an inadequate measure of the multiple aspects of obesity. Type 2 diabetes may simply identify women whose histories and patterns of obesity are most strongly associated with endometrial cancer risk.

Another possibility is that diabetes is associated with endometrial cancer, and BMI is on the causal pathway. In this model, the metabolic imbalance that underlies diabetes commonly results in high BMI. High BMI, with all of its effects on hormone levels, is not a confounder but an intermediate step on the causal pathway between diabetes and cancer. As such, it would not be appropriate to adjust for BMI.

Finally, if diabetes confers a modest risk of endometrial cancer, independent of obesity, at least two mechanisms are plausible. One is that insulin acts to increase unopposed estrogen levels. In postmenopausal women, the ovaries no longer produce significant amounts of estrogen or progesterone, and most estrogen is produced through aromatization of androstenedione to estrone in adipose tissue (4). The adrenal glands are the major source of androsteinedione and androgens in women, but the ovaries also contribute to the pool of androgens (38). There is evidence that insulin stimulates ovarian testosterone release, and thus hyperinsulinemia associated with diabetes may increase estrogen levels (38–41). It has been hypothesized that insulin decreases the levels of circulating SHBG, thus increasing free circulating hormones levels (41, 42), and there is evidence from cultured liver cells that insulin inhibits production of SHBG (43). Higher levels of urinary estrogens have been reported in postmenopausal diabetic women compared with nondiabetic women after adjustment for body weight (38, 44), although few studies have examined the subject.

A second proposed mechanism is that insulin decreases hepatic IGFBP-3 and consequently increases circulating IGF-I. There are IGF-I receptors in the endometrium, and IGF-I stim-

ulates cell proliferation *in vitro* (12–16). Insulin is also a weak analogue of IGF-I in the endometrium (15, 16). In addition, IGFBP-3 may have a regulatory role in cell growth control and cancer, apart from its effect on IGF-I (45).

Mechanism(s) by which obesity itself raises risk for endometrial cancer are not fully elucidated. Potischman *et al.* (10), suggested that increased estrogen levels alone are not sufficient to explain the positive association of endometrial cancer with BMI. If IGF-I or insulin is related to development of endometrial cancer, then examining the diabetes-endometrial cancer association may not be informative because many individuals who are insulin resistant and have higher than normal insulin levels are not diabetic. Troisi *et al.* (11) found no significant differences in C-peptide levels between endometrial cancer cases and controls, suggesting that the effect of obesity on endometrial cancer risk is not mediated through high insulin levels.

Future research, particularly prospective studies with biological samples, could be very helpful in answering questions aimed at clarifying these mechanisms. Direct measures of sex hormones, SHBG, IGFBP-3, insulin, IGF-I, and other growth factor levels could be used to address questions regarding the mechanisms underlying the obesity-endometrial cancer association and the diabetes-endometrial cancer association.

Based on the current analyses, we conclude that diabetes does not increase the risk of endometrial cancer in women with a BMI $\leq$ 27.4 kg/m^2 and may confer a modest additional risk to women with a BMI $>$ 27.4 kg/m^2. Even if diabetes confers additional risk to obese women, a very large risk is conferred by obesity itself. Obesity prevention and treatment remain the most obvious routes for primary prevention of endometrial cancer and type 2 diabetes.

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