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Diabetes, Body Size, and Risk of Endometrial Cancer

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Data from a population-based case-control study of Wisconsin women were used to evaluate the relation of diabetes to the risk of endometrial cancer on the basis of body mass index (BMI). Cases (n = 723) were identified from a statewide tumor registry; controls (n = 2,291) were selected randomly from population lists. Diabetes status, weight, height, and other factors were ascertained by telephone interview. Subjects were categorized as not overweight (BMI, <29.1), overweight (BMI, 29.1–31.9), or obese (BMI, >31.9) according to the BMI distribution of middle-aged white women in the Second National Health and Nutrition Examination Survey. Joint associations between diabetes status, BMI, and endometrial cancer were evaluated using unconditional logistic regression models that controlled for age, parity, use of hormone replacement therapy, education, and smoking. Compared with persons without diabetes, those with diabetes had an adjusted odds ratio of 1.86 (95% confidence interval (CI) 1.37–2.52) for endometrial cancer. This association was modified by BMI (p interaction = 0.04). Compared with nonoverweight nondiabetic subjects, nonoverweight and overweight women who reported diabetes had nonsignificant elevated risks of endometrial cancer (nonoverweight, odds ratio (OR) = 1.10, CI 0.66–1.86; overweight, OR = 1.58, CI 0.81–3.05). In contrast, elevated risk estimates were observed for obese diabetic women (OR = 2.95, CI 1.60–5.46). These data contradict earlier reports and suggest that diabetes confers no additional risk of endometrial cancer in women who are neither overweight nor obese. *Am J Epidemiol* 1998;148:234–40.

body mass index; case-control studies; diabetes mellitus, non-insulin-dependent; endometrial neoplasms; logistic models; obesity in diabetes

Diabetes is hypothesized to be a risk factor for endometrial cancer, although epidemiologic data are inconclusive. Early studies reporting crude risk estimates (1–5) or simple percentages of incident cases with diabetes compared with the population prevalence of diabetes (6) generally show a greater prevalence of diabetes in subjects with this cancer, although results are not consistent (7–9). Studies that have adjusted for body mass report positive (10, 11) or null (12, 13) associations. Because non-insulin-dependent diabetes mellitus (NIDDM) is often associated with an elevated body size (14), and because body size consistently demonstrates strong positive associations with endometrial cancer (15), it is of interest to determine whether the relation between diabetes and endometrial cancer is due, in part, to associations with body size. If other metabolic characteristics of diabetes, such as hyperinsulinemia, have an etiologic role in endometrial cancer independent of body weight, as has been hypothesized for colorectal (16, 17) and breast (18, 19) cancers, then the risk associated with having diabetes should be evident in all strata of body weight. The aim of our analysis was to evaluate the modifying effect of body size on the relation between self-reported diabetes status and risk of endometrial cancer.

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Abbreviations: BMI, body mass index; CI, confidence interval; NIDDM, non-insulin-dependent diabetes mellitus; OR, odds ratio.

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MATERIALS AND METHODS

Participants

All participants were female residents of Wisconsin aged 40–79 years. Incident cases of invasive endometrial cancer (diagnosed between 1991 and 1994) were identified by a statewide mandatory cancer registry. According to an institutionally approved protocol, we contacted the physician of record for each eligible case by mail to obtain permission to approach the subject. Eligibility was limited to cases with listed telephone numbers, drivers' licenses verified by self-report (if less than aged 65 years), and Medicare cards (if more than aged 65 years). A total of 745 cases (87 percent of those eligible) were interviewed. The reasons for nonparticipation included physician refusal (n = 6), subject refusal (n = 53), failure to locate (n = 2), and

death (n = 50). Of those cases interviewed, 98 percent had histologic confirmation of invasive endometrial cancer.

Community controls were selected randomly from lists of licensed drivers (if less than aged 65 years) and Medicare beneficiary files compiled by the Health Care Financing Administration (if aged 65–79 years). The controls were selected at random to yield an age distribution similar to that of the cases, and the controls met the eligibility criterion of having a listed telephone number. Controls were eligible for the study if they reported no previous diagnosis of uterine cancer.

Of the 4,362 eligible controls, 521 (11.9 percent) refused to participate, 35 (0.8 percent) could not be located, and 88 (2.0 percent) were deceased. A total of 3,718 (85.2 percent) completed the study interview. After they were interviewed, 1,304 controls who reported a history of hysterectomy and six for whom interviews were determined to be unreliable were excluded. In all, data on 2,408 controls were available for analysis.

Data collection

Before they were contacted by telephone, cases and controls received letters briefly describing the study. The 45-minute structured interview elicited information on numerous factors prior to an assigned reference date. For cases, it was the date of diagnosis of endometrial cancer. For comparability, controls were assigned a reference date that corresponded to the average date of diagnosis for similarly aged cases (within 5-year strata) interviewed during the same month. Trained study staff conducted telephone interviews without prior knowledge of subjects' disease status. When interviewing 82 percent of the cases and 96 percent of the controls, the interviewer remained unaware of the subject's case-control status until the interview ended.

Diabetes status was ascertained by asking subjects whether, prior to the assigned reference date, their physician had ever told them that they had diabetes. Age at diabetes diagnosis was also queried. Subjects were asked about their height when they were in their twenties and about their weight and height prior to the assigned reference date, as well as about their minimum and maximum weights since age 20 years. In addition, the interview covered reproductive history, exogenous hormone use, medical history, smoking history, and demographic factors.

Information on diabetes status was missing for six cases and 67 controls; of the remaining subjects, data on weight and/or height were incomplete for 16 cases and 50 controls. Thus, for this analysis, complete information was available for 723 cases and 2,291 controls.

Analyses

Duration of diabetes was calculated as the difference between the subject's current age and age at diagnosis of diabetes. Those without diabetes were assigned a duration of 0. Duration was divided into tertiles based on the distribution of controls with diabetes. A fourth category of duration included three diabetic subjects (one case, two controls) who did not know their age at diagnosis. Body mass index (BMI) was computed using current weight and maximum height (weight (kg)/height^2 (m^2)). Subjects were categorized as not overweight (BMI, <29.1), overweight (BMI, 29.1–31.9), or obese (BMI, >31.9) according to the BMI distribution of middle-aged white women (aged 55–64 years) in the Second National Health and Nutrition Examination Survey of 1976–1980 (20). The lower and upper ends of the "overweight" category correspond to the 75th and 85th percentiles, respectively, of this population. Age was defined as the age at diagnosis or reference date. Parity was the sum of livebirths and stillbirths.

Multivariable logistic regression was used to compute odds ratios and 95 percent confidence intervals (21). The models included terms for established and potential risk factors including BMI, age (continuous), smoking status (never, former, current), use of hormone replacement therapy (never, former, current), parity (four levels), and education (four levels). The interaction between BMI and diabetes status was evaluated by including a term representing the product of the continuous BMI variable and the dichotomous diabetes variable. The model that includes indicator variables for joint classification of subjects according to diabetes status and BMI category also includes continuous BMI to control for residual confounding.

RESULTS

The prevalence of diabetes was significantly higher among cases (12 percent) than among controls (6 percent) (chi-square p = 0.0001). Cases were also significantly heavier than controls (mean BMI, 29.8 vs. 26.3 kg/m^2; Student's t test p = 0.0001).

Selected characteristics of cases and controls, according to diabetes status, are shown in table 1. Compared with controls who had diabetes, cases who had diabetes were heavier (p = 0.0001) and had a shorter duration of diabetes, although this latter difference was not statistically significant (p = 0.13). The ages of diabetic cases and controls were not different (p = 0.45).

Table 2 shows multivariable-adjusted odds ratios of endometrial cancer according to diabetes status, duration of diabetes, BMI category, and other covariates. Diabetes was associated with an almost twofold in-

TABLE 1. Selected characteristics (%) of women with endometrial cancer (n = 723) and population controls (n = 2,291) according to diabetes status,* Wisconsin, 1991–1994

	Diabetes status			
	Cases		Controls	
	Present (n = 87)	Absent (n = 636)	Present (n = 143)	Absent (n = 2,148)
Age (years)				
40–49	8	12	1	3
50–59	11	26	18	32
60–69	52	32	52	39
70–79	29	30	29	26
Mean†	64.8 (8.7)	62.6 (10.1)	65.7 (7.3)	63.1 (8.4)
Duration of diabetes (years)				
≤5	37		33	
6–13	38		34	
≥14	25		33	
Mean†	9.8 (9.0)	0	11.9 (10.4)	0
Body mass index (kg/m²)				
Not overweight	23	59	56	76
Overweight	18	13	22	12
Obese	59	28	22	12
Mean†	34.5 (7.0)	29.1 (7.4)	29.1 (5.5)	26.1 (5.0)

* For those subjects reporting a history of diabetes, 86 cases and 141 controls reported an age at diagnosis.
† Standard deviation in parentheses.

crease in risk of endometrial cancer (odds ratio (OR) = 1.86, 95 percent confidence interval (CI) 1.37–2.52). Duration of diabetes (compared with no diabetes) was associated with an increased risk of endometrial cancer that decreased as duration increased (p trend = 0.001). BMI was associated with a risk of endometrial cancer. Compared with having a low BMI (<29.1 kg/m^2), being overweight was associated with an odds ratio of 1.60 (95 percent CI 1.23–2.08), and obesity was associated with an almost fourfold increase in risk (OR = 3.88, 95 percent CI 3.11–4.85).

The association between diabetes and endometrial cancer was modified by BMI (p interaction = 0.04). To investigate this modifying effect further, joint associations between diabetes status and BMI category were evaluated (table 3). Compared with those who did not have diabetes and were not overweight, diabetics of moderate body size (BMI, <29.1) had a nonsignificant elevated risk (OR = 1.10, 95 percent CI 0.66–1.86). Overweight subjects with diabetes had a higher risk of endometrial cancer, although this association was not statistically significant (OR = 1.58, 95 percent CI 0.81–3.05). However, obese subjects with diabetes had a substantially increased risk (OR = 2.95, 95 percent CI 1.60–5.46). This odds ratio is greater than the expected joint effects estimated from the additive (1.10 + 1.15 − 1.0 = 1.25) and multiplicative (1.10 × 1.25 = 1.38) models.

DISCUSSION

Data presented here suggest that women with diabetes who are not obese have no increased risk of endometrial cancer compared with nonoverweight women without diabetes. For obese women, having diabetes is associated with an approximately threefold increase in risk above that attributed to body size alone.

In our study, the overall twofold increase in risk associated with diabetes is similar to risk estimates reported by others who adjusted for body size (10, 11). The prevalence of diabetes among cases in our population was similar to that reported by Brinton et al. (11) and Spengler et al. (5). Others have reported both a higher (1, 4, 10) and a lower (3, 7, 8, 13) prevalence of diabetes in their case populations. A limitation of most studies, including this one, is that the type of diabetes is not known. Among the diabetic subjects in our study, only 3.9 percent (one case, eight controls) reported that their diabetes was diagnosed before age 30 years; for 73 percent, it was diagnosed at age 50 years or older. Thus, the majority of this sample is likely composed of persons diagnosed with NIDDM. Excluding the early-onset subjects did not meaningfully alter the results (adjusted diabetes: OR = 1.96, CI 1.44–2.68). La Vecchia et al. (10) noted that an increased risk of endometrial cancer was apparent only for women with adult-onset diabetes (i.e., NIDDM).

Some limitations should be considered when interpreting our results. A high percentage of women participated in the study (87 percent of cases and 85 percent of controls), which suggests that selection bias, if any, was limited. However, nondiabetics may have been misclassified. It is estimated that about 50 percent of the population with diabetes is undiagnosed

TABLE 2. Odds ratios of endometrial cancer in cases (n = 723) and population controls (n = 2,291) according to diabetes status, duration of diabetes, body mass index, and other covariates, Wisconsin, 1991–1994

	Cases	Controls	Multivariable-adjusted OR*,†	95% CI*
Diabetes				
Absent	636	2,148	1.00	
Present	87	143	1.86	1.37–2.52
Duration of diabetes (years)				
0 (no diabetes)	636	2,148	1.00	
≤5	32	46	2.14	1.30–3.51
6–13	33	48	1.99	1.22–3.24
≥14	21	47	1.40	0.80–2.43
Body mass index (kg/m²)				
Not overweight	393	1,714	1.00	
Overweight	101	293	1.60	1.23–2.08
Obese	229	284	3.88	3.11–4.85
Smoking status				
Never	432	1,238	1.00	
Former	222	697	0.86	0.71–1.05
Current	69	356	0.62	0.46–0.83
Use of hormone replacement therapy				
Never	405	1,566	1.00	
Former	177	422	1.86	1.50–2.32
Current	141	303	2.49	1.94–3.20
Education				
Some high school	125	381	1.00	
Completed high school	355	1,176	0.80	0.62–1.04
Some college	153	442	0.89	0.66–1.20
≥4 years of college	90	292	0.74	0.53–1.05
Parity				
0	123	235	1.00	
1–2	263	674	0.77	0.59–1.02
3–4	239	855	0.51	0.39–0.68
≥5	98	527	0.31	0.23–0.43

* OR, odds ratio; CI, confidence interval.
† Estimates adjusted for age and other variables.

TABLE 3. Adjusted odds ratios* of endometrial cancer in cases (n = 723) and population controls (n = 2,291) by combined categories of body mass index and diabetes status,† Wisconsin, 1991–1994

Diabetes	Body mass index category											
	Not overweight				Overweight				Obese			
	Cases	Controls	OR‡	95% CI‡	Cases	Controls	OR	95% CI	Cases	Controls	OR	95% CI
Absent	373	1,633	1		85	262	0.91	0.66–1.27	178	253	1.15	0.75–1.77
Present	20	81	1.10	0.66–1.86	16	31	1.58	0.81–3.05	51	31	2.95	1.60–5.46
p interaction = 0.04												

* Adjusted for body mass index (continuous), age (continuous), smoking status (never, former, current), education (categorical), parity (categorical), and use of hormone replacement therapy (never, former, current).
† Beta coefficients (standard errors) for indicator variables and interaction term: diabetes absent/overweight: −0.09 (0.17); diabetes absent/obese: 0.14 (0.22); diabetes present/not overweight: 0.10 (0.27); diabetes present/overweight: 0.45 (0.34); diabetes present/obese: 1.08 (0.31); diabetes status × continuous body mass index interaction term: 0.06 (0.03).
‡ OR, odds ratio; CI, confidence interval.

(22). Because study participants were sampled from the general population, it is likely that an appreciable number had diabetes but were unaware of their condition. In addition, because overweight and obese persons are more likely to have undiagnosed diabetes (23), the modifying effect of BMI may be partly attributable to misclassification of diabetes status among these participants.

Another limitation is that our results may reflect bias due to increased surveillance of persons with diabetes. A similar bias was posited by Horwitz and Feinstein (24), whereby women on hormone replace-

ment therapy were subject to increased surveillance that may have resulted in earlier detection of asymptomatic endometrial adenocarcinoma. To evaluate the possibility that diabetics were more likely to receive a diagnosis of endometrial cancer, we determined whether cases were diagnosed with an earlier stage of the disease if they were diabetic. A similar proportion of cases with diabetes (83 percent) and without diabetes (78 percent) were diagnosed with localized disease ($p = 0.4$). Thus, more frequent health surveillance of persons with diabetes is unlikely to have introduced bias into these analyses. Furthermore, there is no routine screening test for endometrial cancer; 90 percent of women with this cancer present with postmenopausal bleeding (25). Thus, increased surveillance is unlikely.

The strong interaction between BMI and diabetes observed in this study supports the hypothesis that hyperinsulinemia may be an etiologic factor in endometrial carcinogenesis, as has been proposed for other cancers (16–19, 26–29). Potischman et al. (30) have suggested that insulin may be a relevant factor in explaining the strong associations between body size, adiposity, and risk of endometrial cancer. They report that after controlling for endogenous sex hormones and sex hormone binding globulin, risk estimates for measures of body size and adiposity remained essentially the same, and they suggest that unopposed estrogen alone may not explain fully the body size/body fat associations with endometrial cancer. Interestingly, a subsequent investigation in this population using measurements of C-peptide (an indicator of insulin secretion) did not support an etiologic role of hyperinsulinemia (31). In women reporting no history of diabetes, no association was observed between C-peptide levels and risk of endometrial cancer after adjusting for BMI, waist-to-thigh ratio, and other factors (31).

Pathophysiologic levels of insulin may be causally related to endometrial cancer as a result of several interrelated mechanisms. Insulin may act as an endometrial mitogen by augmenting the proliferative effects of insulin-like growth factors (32–36). However, an understanding of the role of growth factors in endometrial carcinogenesis is incomplete (37), and data from human studies on the relation between hyperinsulinemia and the insulin-like growth factor system in the etiology of endometrial cancer remain inconclusive (38). Insulin may also operate through its associations with decreased levels of sex hormone binding globulin and increased levels of testosterone (29, 39–42), resulting in elevated levels of free estrogen. With regard to the hyperinsulinemia hypothesis, use of sulfonylureas, hypoglycemic agents that stimulate insulin secretion (43), is of interest.

The modifying effect of BMI on the relation between diabetes and endometrial cancer observed in this study may be a marker of some of the metabolic abnormalities that are highly correlated with body size and adiposity (44–46). NIDDM is the result of complex interactions between impaired insulin secretion, reduced glucose disposal in insulin-sensitive tissues, and dysregulation of hepatic glucose production (47). Large interindividual variation exists in the metabolic abnormalities that precede glucose intolerance and hyperglycemia. It is generally believed that insulin insensitivity with compensatory increases in insulin secretion precedes hyperglycemia and that prolonged hypersecretion of insulin leads to pancreatic beta cell dysfunction with a concomitant decrease in insulin secretion (47, 48). Insulin sensitivity (49) and insulin levels (50, 51) appear to vary according to body size, although there is much heterogeneity in this association (52). Thus, women with diabetes who are not obese may not have an increased risk of endometrial cancer, because they were not exposed to the same level of insulin as obese diabetic women. In our study, nonoverweight subjects reported significantly lower minimum and maximum weights since age 20 years compared with overweight and obese participants (data not shown). The lower weights maintained by nonoverweight diabetic subjects may have resulted in relatively lower levels of circulating insulin compared with overweight and obese diabetic subjects.

In this study, a long duration of diabetes ($\geq$14 years) was not associated with a risk of endometrial cancer. This finding is intriguing given the strong age-independent relation between duration and other chronic diseases (53–57). Concerning the insulin hypothesis, it may be expected that endometrial cancer risk would decrease with increasing duration given the inverse association between duration and insulin secretion in persons with NIDDM. Our data suggest this trend. However, meaningful associations would be difficult to detect without information on the use of hypoglycemic agents. These drugs act differently to reduce glucose levels (58), and mode of action may be relevant to circulating insulin levels. Alternatively, it is possible that among subjects with diabetes of long duration, weight loss associated with poor glycemic control may offset the adverse effects of other metabolic aspects of diabetes. In this study, a modest age-independent, inverse correlation between BMI and duration was statistically significant in diabetic subjects ($r = -0.23$, $p = 0.0005$).

Important characteristics of diabetes that may differ between cases and controls and may be related to weight, including measures of abdominal adiposity, use of hypoglycemic agents, levels of endogenous

insulin, and degree of glycemic control, could not be accounted for in our study. This limitation makes it difficult to separate the effects of weight from other metabolic aspects of diabetes when determining its relation to risk of endometrial cancer. Future studies will benefit from measuring these parameters where possible. Nevertheless, our data show that the relation of diabetes to endometrial cancer is modified by body size. For women who are not obese, diabetes itself appears to confer no additional risk.

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