Endometrial carcinoma and diabetes revisited

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Summary

Objective: To investigate whether endometrial adenocarcinomas are intrinsically different in diabetic as compared to non-diabetic patients.

Methods: A series of 208 patients with histologically confirmed endometrial adenocarcinomas were divided into groups of diabetic (n = 63) and non-diabetic (n = 145) patients. The two groups were compared in terms of tumor morphology, FIGO stage, clinical risk factors and 12-year survival.

Results: A history of a second neoplasia was significantly more frequent in diabetic than in non-diabetic patients (p = 0.001), but other endometrial cancer associated characteristics, such as tumor morphology, FIGO stage, obesity, hypertension, nulliparity, estrogen use and menopausal status did not differ between the groups. More importantly, the two groups had a similar 12-year survival rate (p = 0.8742).

Conclusions: A second neoplasia occurred significantly more frequently in diabetic than in non-diabetic patients with endometrial carcinoma, but long-term survival and other clinical and histological features were the same in the two groups. These results indicate that endometrial adenocarcinoma is not intrinsically different in diabetic patients.

Key words: Diabetes mellitus; Endometrial carcinoma; Risk factors; Survival.

Introduction

Endometrial adenocarcinoma is by far the most common gynecological malignancy in industrialized countries and its frequency is rising [1-3]. It was estimated that approximately 6,000 women died from this tumor in the United States in 1997 [2]. The disease has been associated with several risk factors, the most important being old age, obesity, hypertension and diabetes mellitus [1-5]. Indeed, the unprecedented increase in the incidence of endometrial carcinoma can be largely attributed to the rising frequency of diabetes and obesity, which is currently spreading in developing countries [1-3, 6].

The traditional association of diabetes mellitus with endometrial adenocarcinoma has been established from both case-control and cohort studies [7-19]. However, since most diabetic patients have type 2 diabetes, the form of disease which is most commonly linked to obesity [6, 22], the increased risk for endometrial carcinoma, allegedly conferred by diabetes, could well be attributed to obesity [3, 20, 21]. Results have been contradictory [3, 11, 18-21]. Some investigators demonstrated an increased relative risk for endometrial carcinoma in patients with diabetes, even after adjustment for obesity [15, 18, 19], while others reported no significant risk in diabetics with normal weight [3, 17, 21].

Whether increasing or not the risk for endometrial adenocarcinoma, diabetes mellitus has also been claimed to have an adverse impact on the prognosis of patients who suffer from the disease [23-25]. In some, though by no means all [26], studies, this has been associated with deep myometrial invasion [23].

Is, after all, endometrial adenocarcinoma intrinsically different in diabetic patients? The current study was set to investigate this question. In particular, it examines if there is a difference between diabetic and non-diabetic patients in terms of pathological features, clinical risk factors, and overall survival. Risk factors for carcinoma of the endometrium have, to our knowledge, not been examined separately in diabetic vs non-diabetic patients.

Materials and Methods

This study included 208 women with histologically confirmed endometrial adenocarcinoma. Patients were divided into two groups according to their diabetes mellitus (DM) status. Thus, 63 patients were diabetic and 145 were non-diabetic. Diabetes mellitus was defined as hypoglycemic treatment or fasting hyperglycemia exceeding 126 mg/dl, in accordance with the American Diabetes Association criteria [27].

Other endometrial cancer-associated conditions that were sought included the presence or absence of hypertension and obesity. Hypertension was defined as antihypertensive treatment or systolic pressure higher than 140 mm Hg and/or diastolic pressure higher than 90 mm Hg on three separate occasions [29]. Obesity was defined as a body mass index (calculated as weight in kilograms divided by the square of height in meters) $\geq$ 30 kg/m^2 [6].

Age at diagnosis, pre/postmenopausal status, smoking habits (smokers vs non-smokers), number of deliveries, estrogen use and past medical history of a second malignant neoplasia were also recorded.

The histological type and the degree of tumor differentiation were assessed as indicated previously [30, 31]. The depth of myometrial invasion was evaluated as penetration into the inner or outer half [28]. Surgical staging was according to FIGO [28].

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Thirty-eight patients were lost to follow-up. Two patients died of concomitant cancer (breast and colon, respectively), one patient died of pneumonia, one patient died in a car accident and 23 patients died of cardiovascular disease (myocardial infarction, congestive heart failure and stroke). The remaining 143 patients were evaluated for survival and mortality exclusively due to endometrial carcinoma.

Statistical analysis was performed using SPSS (Statistical Package for Social Sciences) 11.0. The chi-square test (with Yates' correction for 2 x 2 contingency tables) and Fisher's exact test were used as appropriate for qualitative variables. Normally distributed quantitative variables were analyzed by the unpaired t-test, while variables without normal distribution were analyzed by Mann-Whitney's U test. Cancer-specific survival was calculated from diagnosis of cancer until death or else until 31 December, 2004. The Kaplan-Meier method was used to compare survival rates. Significance was defined at the 5% level ($p < 0.05$).

Results

The mean age of the patients at diagnosis was 65.98 ± 9.55 years. Epidemiological risk factors for endometrial carcinomas in our series and their frequency in each group are shown in Table 1. A past medical history of a second malignant neoplasia was significantly ($p = 0.001$) higher in patients with diabetes compared to those without. There was no other difference in other clinical risk factors between the two groups. Similarly, the histopathological features of the tumors ($p = 0.77$) and the FIGO stage of disease ($p = 0.931$) were almost identical in the two groups of patients (Table 2).

Endometrial cancer-specific survival data were available for 143 patients (46 diabetics, 97 non-diabetics). Survival did not differ significantly between the two groups of endometrial cancer patients (log-rank test chi squared = 0.0251, df = 1, $p = 0.8742$). Kaplan-Meier survival curves are shown in Figure 1.

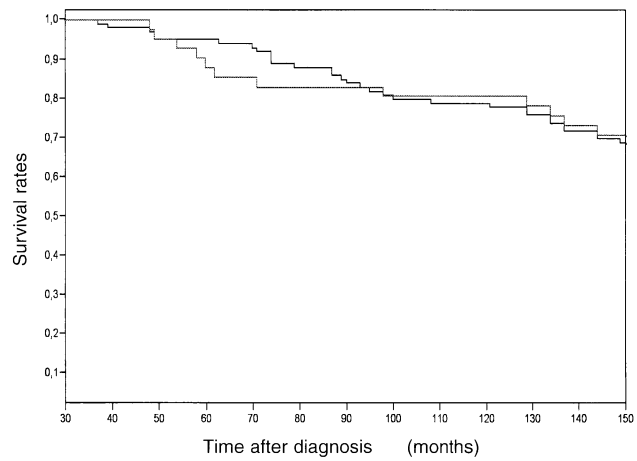
Table 1. — *Epidemiological risk factors in the two groups.*

Risk factor	All patients (N = 208)	Patients with diabetes (N = 63)	Patients without diabetes (N = 145)	p value*
Obesity	114 (54.8%)	33 (52.38%)	81 (55.86%)	p = 0.755
Hypertension	108 (51.92%)	32 (50.8%)	76 (52.41%)	p = 0.949
Estrogen use	3 (1.44%)	1 (1.59%)	2 (1.38%)	p = 1.0**
Menopausal state	178 (85.58%)	55 (87.3%)	123 (84.83%)	p = 0.801
History of a second malignancy	32 (15.38%)	22 (34.92%)	10 (6.89%)	p = 0.001
Nulliparity	49 (23.56%)	15 (23.8%)	34 (23.44%)	p = 1.0
BMI (mean ± SD, kg/m^2)	27.7 ± 4.1	26.98 ± 3.32	28.11 ± 3.18	p = 0.41
Age at diagnosis (mean±SD, yrs)	65.98 ± 9.55	65.16 ± 8.82	66.82 ± 8.93	p = 0.214
Age at menopause (mean±SD, yrs)	51.02 ± 4.10	51.16 ± 3.53	50.55 ± 3.71	p = 0.264
Number of deliveries (median, range)	1 (0-4)	1 (0-4)	1 (0-4)	p = 0.8

*Endometrial cancer patients with diabetes vs endometrial cancer patients without diabetes.
**Fisher's exact test.

Table 2. — *Histopathological features of endometrial cancer patients with and without diabetes.*

	Cases N (%)	Diabetic patients	Non-diabetic patients
Tumor cell type (p = 0.770)			
Endometrioid	182 (87.5%)	53 (84.1%)	129 (89.0%)
Serous papillary	14 (6.7%)	5 (7.9%)	9 (6.2%)
Clear cell	10 (4.8%)	4 (6.4%)	6 (4.1%)
Undifferentiated	2 (1.0%)	1 (1.6%)	1 (0.7%)
Tumor differentiation (p = 0.37)			
G1	166 (79.8%)	52 (82.53%)	114 (78.6%)
G2	16 (7.7%)	6 (9.52%)	10 (6.9%)
G3	26 (12.5%)	5 (7.9 %)	21 (14.5%)
Depth of myometrial invasion (p = 0.371)			
Inner half	169 (81.25%)	54 (85.7%)	115 (79.3%)
Outer half	39 (18.75%)	9 (14.3%)	30 (20.7%)
FIGO stage (p = 0.931)			
I	115 (55.29%)	34 (54%)	81 (55.8%)
II	71(34.13%)	21 (33.3%)	50 (34.5%)
III	19 (9.13%)	7 (11.1%)	12 (8.3%)
IV	3 (1.44%)	1 (1.6%)	2 (1.4%)



Solid line: Diabetic patients (N = 46).
Dashed line: non-diabetic patients (N = 97).

Figure 1. — Kaplan-Meier survival curves in the two groups of patients ($p = 0.8742$).

Discussion

An association between diabetes mellitus and carcinoma of the endometrium has been shown in many studies [1-4, 6, 7-21], the increased risk for endometrial carcinoma being attributed to hyperinsulinemia [1, 3, 19, 21]. Yet, it is not clear whether the elevated plasma insulin concentrations lead to an estrogen increase, via a mechanism of accelerated androgen production in the ovaries and peripheral aromatisation in adipose tissue [1, 3, 19, 21], or whether hyperinsulinemia renders more estrogen available by reducing the sex hormone binding globulin [1, 3, 19, 21]. Others would argue that insulin enhances mitogenesis in the endometrium, both directly and through the increase of insulin growth factor-1 [19, 21].

Another question that has not been answered satisfactorily is whether endometrial carcinoma is intrinsically different in diabetic patients compared to non-diabetics – this particular issue was addressed in the current study. In fact, there was no significant difference in the prevalence of obesity between diabetic and non-diabetic patients, and BMI did not differ significantly between the two groups. Although a higher incidence of obesity might be anticipated among endometrial cancer patients with diabetes [6, 22, 27], our patients without diabetes were equally obese. This finding is in accord with other studies highlighting the importance of obesity as a major independent risk factor in the development of endometrial adenocarcinoma [6, 21, 32-36]. In this context, diet-induced weight loss has been shown to substantially reduce the risk of malignant endometrial disease [36].

With the exception of the presence of a second malignancy, occurring significantly more commonly in diabetic than in non-diabetic patients, none of the known clinical risk factors was found to be more frequent in either of the groups. A personal history of a second malignancy has been shown more frequently in patients with endometrial carcinoma compared to controls [1, 16, 33], but such a tendency in diabetic vs non-diabetic patients with malignant endometrial disease has not been previously reported. Affected organs included mainly the breast, colon and ovaries. Our finding is in line with recent epidemiological evidence pointing to a link between diabetes and risk of cancer in various organs, as reviewed by Mori *et al.* [37].

With regard to pathological features, such as type of endometrial carcinoma, differentiation and depth of myometrial invasion, these occurred with an almost similar frequency in the two groups, as did FIGO stage of disease. This is in agreement with some of the most recent studies [26, 38], although others associated diabetes with deep myometrial invasion and high incidence of lymph node metastasis [23].

Given that the two study groups are comparable in terms of clinical and pathological features, including FIGO stage, it is plausible that any difference in survival would reflect the impact of diabetes itself. This was further ensured by excluding patients who died of causes other than endometrial carcinoma from survival analysis. For, indeed, diabetic patients have an increased cardiovascular morbidity and mortality, so that any excess in the overall mortality might represent deaths from cardiovascular disease rather than to cancer itself. Again, it was found that endometrial cancer-specific survival did not differ significantly between the two groups, providing substantial evidence against a role of diabetes as an independent adverse prognostic factor. Results from other institutions are contradictory, with some voices in dissent [25, 40] and others in agreement [26, 39]. Still others found that diabetes was a significant predictor of poor survival in univariate, but not in multivariate analysis [24] and attributed their finding as dependent on the presence of adverse pathological features such as deeper myometrial invasion and higher incidence of lymph node metastasis [24]. Moreover, recurrence of endometrial cancer was not associated with diabetes [24].

Interestingly, Troisi *et al.* found no association between serum C-peptide levels and endometrial cancer, thus casting some doubt on the insulin-endometrial cancer hypothesis [41]. More importantly, hyperinsulinemia is a feature of type 2, and not of type 1, diabetes [27] and, as Parazzini and associates indicated, it is only type 2, and not type 1, diabetes which is connected with increased risk of endometrial cancer [18]. Furthermore, insulin resistance with consequent hyperinsulinemia is closely linked to obesity [6, 22, 32]. Hence, the direct association of diabetes with endometrial carcinoma, irrespective of obesity, is becoming increasingly questionable [3, 20, 21].

Misdiagnosis of diabetes or other risk factors is unlikely to have occurred in our material, since all patients were hospitalized and uniform diagnostic criteria were employed. However, we were not able to reliably distinguish between the two types of diabetes because data from patient history were retrospective. This might be of importance since some differences in risk factor profile between type 1 and type 2 diabetes have been suggested, despite the lack of universal agreement [18, 19].

Conclusion

A medical history of cancer was significantly more frequent in diabetic than in non-diabetic patients with endometrial carcinoma. Other associated medical conditions and pathological features, however, were almost similar and so was endometrial cancer-specific survival. It would appear, therefore, that endometrial carcinoma does not essentially differ between diabetic and non-diabetic patients. The implication for clinical practice is that treatment options should not be influenced by the presence of diabetes. Certainly, further studies incorporating data on diabetes duration, type of diabetes, chronic diabetic complications and glycemic control are awaited to enrich our knowledge on the impact of diabetes on this gynecological malignancy.

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