Research Article

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Type II Diabetes Mellitus and the Incidence of Epithelial Ovarian Cancer in the Cancer Prevention Study-II Nutrition Cohort

Susan M. Gapstur, Alpa V. Patel, W. Ryan Diver, Janet S. Hildebrand, Mia M. Gaudet, Eric J. Jacobs, and Peter T. Campbell

Abstract

Background: Despite consistent associations of type II diabetes mellitus with hormonally related cancers such as breast and endometrium, the relation between type II diabetes mellitus and ovarian cancer risk is unclear.

Methods: Associations of type II diabetes mellitus status, duration, and insulin use with epithelial ovarian cancer overall, and with serous and nonserous histologic subtypes were examined in the Cancer Prevention Study-II Nutrition Cohort, a prospective study of U.S. men and women predominantly aged 50 years and older. Between 1992 and 2007, 524 incident epithelial ovarian cancer cases were identified among 63,440 postmenopausal women. Multivariable-adjusted relative risks (RR) and 95% confidence intervals (CI) were computed using extended Cox regression to update diabetes status and bilateral oophorectomy status during follow-up.

Results: Type II diabetes mellitus status (RR = 1.05; 95% CI, 0.75–1.46) and duration were not associated with epithelial ovarian cancer risk. Although not statistically significantly different ($P_{\text{difference}} = 0.39$), the RR was higher for type II diabetes mellitus with insulin use (RR = 1.28; 95% CI, 0.74–2.24) than for type II diabetes mellitus without insulin use (RR = 0.96; 95% CI, 0.64–1.43). Diabetes seemed to be more strongly associated with nonserous (RR = 1.41; 95% CI, 0.70–2.85) than serous (RR = 0.71; 95% CI, 0.41–1.23) histologic subtypes.

Conclusions: Type II diabetes mellitus was not associated with risk of epithelial ovarian cancer, although higher risks with nonserous subtypes and among insulin users cannot be ruled out.

Impact: Larger studies are needed to clarify associations of type II diabetes mellitus with or without insulin use with risk of ovarian cancer overall and by histologic subtypes. *Cancer Epidemiol Biomarkers Prev; 21(11); 2000–5. ©2012 AACR.*

Introduction

In 2009, the American Cancer Society (ACS) and the American Diabetes Association convened an expert panel to review the evidence on diabetes and cancer risk (1). There was consensus that type II diabetes mellitus is associated with an elevated risk for cancers of the liver, pancreas, endometrium, colon/rectum, breast, and possibly bladder. It also was noted that for less common malignancies, including ovarian cancer, data are limited or absent and more research is needed.

Most ovarian cancers arise from epithelial cells which are classified into serous, endometrioid, clear cell, mucinous, and other histologic subtypes, and there is some evidence of etiologic heterogeneity by histologic subtypes (2). Whether type II diabetes mellitus is associated with the risk of epithelial ovarian cancer is unclear. Results are inconsistent among registry-based studies that compared ovarian cancer incidence or mortality rates for patients hospitalized with diabetes mellitus with rates for the underlying populations (3–9). However, those studies must be interpreted cautiously because of the lack of data on potential confounding factors (e.g., body size), and because analyses did not exclude women who had bilateral oophorectomy. While several case–control (10–12) and prospective cohort studies (13–15) showed no association, 2 other prospective studies showed nonstatistically significant higher risks of ovarian cancer associated with diabetes mellitus (16) and/or impaired fasting glucose (17). None of the prospective studies examined the association of insulin use with risk of ovarian cancer, nor did they update diabetes status during the follow-up period and only one study (14) censored follow-up at the time of bilateral oophorectomy; these 2 sources of bias could attenuate an association due to misclassification over time. No study has examined the relation of diabetes with risk of specific epithelial ovarian cancer subtypes.

Authors' Affiliation: Epidemiology Research Program, American Cancer Society, Atlanta, GA

Corresponding Author: Susan M. Gapstur, Epidemiology Research Program, American Cancer Society, 250 Williams Street, NW Atlanta, GA. Phone: 404-329-5741; Fax: 404-327-6450; E-mail: susan.gapstur@cancer.org

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This analysis examined the associations of type II diabetes mellitus status and duration, and type II diabetes mellitus with and without insulin use with epithelial ovarian cancer incidence in the ACS Cancer Prevention Study (CPS)-II Nutrition Cohort, a prospective study of cancer incidence and mortality among approximately 184,000 U.S. men and women. In addition, the associations of type II diabetes mellitus with risk of histologic subtypes were explored. The CPS-II Nutrition Cohort has the advantage of repeated data collection allowing for updating type II diabetes mellitus status and oophorectomy status during follow-up.

Materials and Methods

Study population

The CPS-II Nutrition Cohort includes 86,402 men and 97,786 women (18), and is a subgroup of approximately 1.2 million participants in the CPS-II mortality cohort established by the ACS in 1982 (19). CPS-II Nutrition Cohort participants resided in 21 states with population-based cancer registries, were predominantly aged 50 years and older, and completed a 10-page self-administered mailed questionnaire in 1992 or 1993. Beginning in 1997, follow-up questionnaires were sent to cohort members every 2 years to update exposure information and ascertain self-reported new cancer diagnoses. Follow-up questionnaire response rates among living cohort members were at least 89%. The Emory University School of Medicine Institutional Review Board (Atlanta, GA) approves the CPS-II Nutrition Cohort.

Excluded from analyses were female participants who were lost to follow-up (i.e., alive in 1997 but did not return the 1997 or any subsequent questionnaires; $n = 3{,}122$), reported a personal history of cancer other than nonmelanoma skin cancer in 1982 or in 1992/1993 ($n = 13{,}091$), were not postmenopausal during follow-up ($n = 1{,}242$), reported a bilateral oophorectomy or unknown oophorectomy at baseline ($n = 16{,}236$), reported unknown diabetes status at baseline ($n = 240$) or inconsistent diabetes status between 1982 and 1992 ($n = 312$), reported insulin use before the age of 30 years ($n = 92$), or reported a diagnosis of ovarian cancer in 1997 that could not be verified through medical or cancer registry records ($n = 11$). A total of 63,440 women were included in the at-risk cohort.

Assessment of diabetes, insulin use, and other risk factors

In the CPS-II Nutrition Cohort, anthropometric, medical, behavioral, and other lifestyle information was ascertained on the mailed questionnaires. Participants were asked on the baseline (1992/1993) questionnaire if they had ever been diagnosed with diabetes by a physician. For the 1997 and all subsequent questionnaires (1999, 2001, 2003, and 2005), the diabetes question was modified to exclude diagnoses of gestational diabetes and participants were asked the year of their diabetes mellitus diagnosis. The duration of diabetes was estimated as described previously (20). On the 1992/93 questionnaire, participants were asked if they had ever used insulin and if so, for how many years. All follow-up questionnaires updated insulin-use status as current, former, or never.

Ascertainment of ovarian cancer cases

This analysis includes incident cases of epithelial ovarian cancers (International Classification of Disease for Oncology, Second and Third Editions site codes C56, C48.1, C48.2, C48.8, and C57.0) that occurred between the date the baseline questionnaire was returned and June 30, 2007. In the at-risk cohort of 63,440 women, 524 incident epithelial ovarian cancer cases were identified, including 368 cases who self-reported on a follow-up questionnaire and were subsequently verified through medical record abstraction or linkage with state cancer registries, and an additional 156 cases who were identified through linkage with the National Death Index (21) of which 105 were also linked to state cancer registries. The sensitivity of self-reported cancer has been estimated to be 93% in this cohort (22).

Statistical analyses

Person-years of follow-up for each participant were calculated as the amount of time from completion of the baseline questionnaire or the questionnaire when menopause was first reported to the date of: (i) diagnosis of epithelial ovarian cancer; (ii) death; (iii) questionnaire date when bilateral oophorectomy was first reported; (iv) questionnaire date when inconsistent diabetes status was reported; (v) the last questionnaire on which the participant did not report an ovarian cancer if they subsequently reported an ovarian cancer that could not be verified; (vi) the return date of last completed questionnaire; or (vii) the end of the follow-up period on June 30, 2007.

Extended Cox regression was used to calculate relative risks (RR) and 95% confidence intervals (CI) for the associations of type II diabetes mellitus, type II diabetes mellitus duration (i.e., <10 years and $\geq$10 years since diagnosis), and type II diabetes mellitus with and without insulin use with risk of epithelial ovarian cancer. Type II diabetes mellitus status, duration, and insulin use were modeled as time-dependent variables updated at the time of each follow-up questionnaire. All models were adjusted for age using the stratified procedure with one-year age strata. Two multivariable models were used to adjust for confounding factors. The first model included race, education, and postmenopausal hormone use. The second model included variables from the first model and body mass index (BMI, weight in kilograms divided by height in meters squared). Oral contraceptive use, number of live births, age at menopause, age at menarche, family history of breast or ovarian cancer, and personal history of hysterectomy or tubal ligation were not included in the multivariable models because they were not associated with type II diabetes mellitus status at baseline nor did they confound the associations of diabetes or insulin use with risk of ovarian cancer. A Wald χ^2test was used to test

whether the RR for diabetes with insulin use differed from that for diabetes without insulin use. Associations of type II diabetes mellitus with risk of serous and nonserous epithelial ovarian cancer also were explored. All analyses were conducted using SAS (version 9.3; SAS Institute Inc.).

Results

The 524 epithelial ovarian cancer cases identified during follow-up included 264 serous, 22 mucinous, 43 endometrioid, 18 clear cell, 18 mixed/Mullerian, and 159 carcinoma not otherwise specified. At baseline, the mean age was 62.2 (SD = 6.45) years among women without type II diabetes mellitus and 63.6 (SD = 6.21) years among women with type II diabetes mellitus.

Although the vast majority of women in this study were white, a higher proportion of women with type II diabetes mellitus compared with those without type II diabetes mellitus in 1992/1993 were black (Table 1). Women with type II diabetes mellitus were more likely to have high

Table 1. Descriptive characteristics by type II diabetes mellitus status in 1992/1993 in the Cancer Prevention Study II Nutrition Cohort

		No Diabetes (*N* = 59,863)	Diabetes (*N* = 3,577)
Variable	**Categories**	***n* (%)**	***n* (%)**
Race	White	58,393 (97.5)	3,397 (95.0)
	Non-white	1,470 (2.5)	180 (5.0)
Education	High school or less	21,443 (35.8)	1,491 (41.7)
	Some college	18,500 (30.9)	1,118 (31.3)
	College grad	19,528 (32.6)	928 (25.9)
	Missing	392 (0.7)	40 (1.1)
BMI (kg/m^2) in 1992	<18.5	1,204 (2)	37 (1)
	18.5–<25	31,339 (52.4)	1,109 (31)
	25–<30	18,131 (30.3)	1,208 (33.8)
	≥ = 30	8,272 (13.8)	1,154 (32.3)
	Missing	917 (1.5)	69 (1.9)
Oral contraceptive use	Never	36,130 (60.4)	2,350 (65.7)
	<5 y	12,110 (20.2)	612 (17.1)
	5+ y	10,023 (16.7)	508 (14.2)
	Unknown y	875 (1.5)	51 (1.4)
	Missing	725 (1.2)	56 (1.6)
Number of live births	Nulliparous	4,242 (7.1)	273 (7.6)
	1–2	19,857 (33.2)	1,115 (31.2)
	≥ = 3	34,619 (57.8)	2,113 (59.1)
	Missing	1,145 (1.9)	76 (2.1)
Age at menopause, y	<45	10,947 (18.3)	750 (21)
	45–54	38,494 (64.3)	2,243 (62.7)
	55+	5,886 (9.8)	431 (12)
	Missing	4,536 (7.6)	153 (4.3)
Age at menarche, y	<12	11,106 (18.6)	834 (23.3)
	12+	47,804 (79.9)	2,680 (74.9)
	Missing	953 (1.6)	63 (1.8)
Family history of breast or ovarian cancer	No	51,260 (85.6)	3,092 (86.4)
	Yes	8,603 (14.4)	485 (13.6)
Hysterectomy	No	47,504 (79.4)	2,703 (75.6)
	Yes	12,359 (20.6)	874 (24.4)
Tubal ligation	No	54,147 (90.5)	3,287 (91.9)
	Yes	5,716 (9.5)	290 (8.1)
Postmenopausal hormone therapy	Never	29,178 (48.7)	1,976 (55.2)
	Current E-only	6,699 (11.2)	289 (8.1)
	Former E-only	7,677 (12.8)	587 (16.4)
	Current E+P	6,538 (10.9)	214 (6)
	Former E+P	1,629 (2.7)	79 (2.2)
	Other/missing	8,142 (13.6)	432 (12.1)

Table 2. Relative risks (RR) and 95% confidence intervals (CI) for associations of type II diabetes mellitus status, type II diabetes mellitus duration and insulin use with risk of epithelial ovarian cancer in the Cancer Prevention Study II Nutrition Cohort, 1992–2007

Diabetes status	Cases, *n*	Person-years	Age-adjusted RR (95% CI)	Multivariable adjusted without body mass index[a] RR (95% CI)	Multivariable adjusted with body mass index[b] RR (95% CI)
No type II DM	485	691,007	1.00	1.00	1.00
Type II DM	39	54,694	0.98 (0.70–1.35)	1.01 (0.73–1.41)	1.05 (0.75–1.46)
Duration type II DM <10 yrs	24	34,095	0.98 (0.65–1.48)	1.01 (0.67–1.52)	1.04 (0.69–1.57)
Duration type II DM ≥10 yrs	15	20,599	0.97 (0.58–1.63)	1.03 (0.61–1.72)	1.06 (0.63–1.79)
			$P_{trend} = 0.89$	$P_{trend} = 0.92$	$P_{trend} = 0.77$
Type II DM without insulin use	26	39,514	0.90 (0.60–1.33)	0.93 (0.62–1.38)	0.96 (0.64–1.43)
Type II DM with insulin use	13	15,180	1.18 (0.68–2.06)	1.24 (0.72–2.16)	1.28 (0.74–2.24)

[a]Multivariable-adjusted models include age, race (white, non-white), education (high school or less, some college, college graduate, missing), and postmenopausal hormone use (never, current estrogen-only, former estrogen-only, estrogen-progestin only, former estrogen-progestin only, other/missing).

[b]Model includes variables in model a and body mass index (<18.5, 18.5–<25.0, 25.0–<30.0, ≥30.0 kg/m^2, missing) in 1992/1993

school or less education, be obese, and report never using postmenopausal hormones.

Type II diabetes mellitus status and type II diabetes mellitus duration were not associated with risk of epithelial ovarian cancer (Table 2). Although not statistically significantly different ($P_{difference} = 0.39$), the risk of ovarian cancer seemed to be higher for women with diabetes who used insulin than for women with diabetes who did not use insulin in multivariable analysis adjusted for BMI.

Exploratory analyses examined associations of type II diabetes mellitus with risk of serous and nonserous histologic subtypes, excluding ovarian cancer cases of unknown histology (Table 3). Diabetes seemed to be more strongly associated with nonserous (RR = 1.41) than serous (RR = 0.71) histologic subtypes.

Discussion

In this large prospective study of postmenopausal women where oophorectomy, diabetes, and insulin use were updated during follow-up, there were no associations of type II DM status or duration with epithelial ovarian cancer risk. However, results do not rule out a possible association between diabetes with insulin use and overall risk of ovarian cancer, or between type II diabetes mellitus status and nonserous ovarian cancer risk.

Few prospective cohort studies have examined the association of type II diabetes mellitus and risk of ovarian cancer. In a recent analysis of the CPS-II cohort of 1.2 million men and women, there was no association between type II diabetes mellitus at baseline in 1982 and ovarian cancer mortality (13). Two other prospective

Table 3. Relative risks (RR) and 95% CI for associations of type II diabetes mellitus status with risk of serous and nonserous epithelial ovarian cancer in the Cancer Prevention Study II Nutrition Cohort, 1992–2007

Diabetes status	Cases, *n*	Person-years	Age-adjusted RR (95% CI)	Multivariable adjusted without body mass index[a] RR (95% CI)	Multivariable adjusted with body mass index[b] RR (95% CI)
Serous ovarian cancer					
No type II DM	250	691,007	1.00	1.00	1.00
Type II DM	14	54,694	0.68 (0.40–1.17)	0.71 (0.41–1.22)	0.71 (0.41–1.23)
Nonserous ovarian cancer					
No type II DM	92	691,007	1.00	1.00	1.00
Type II DM	9	54,694	1.25 (0.63–2.48)	1.29 (0.65–2.57)	1.41 (0.70–2.85)

[a]Multivariable-adjusted models include age, race (white, non-white), education (high school or less, some college, college graduate, missing), and postmenopausal hormone use (never, current estrogen-only, former estrogen-only, estrogen-progestin only, former estrogen-progestin only, other/missing).

[b]Model includes variables in model a and body mass index (<18.5, 18.5–<25.0, 25.0–<30.0, ≥30.0 kg/m^2, missing) in 1992/1993

studies (14, 15) also showed no association of diabetes mellitus or elevated glucose levels with ovarian cancer. Conversely, in a small study with 5 incident ovarian cancer cases among women with diabetes mellitus at baseline, the RR was 2.4 (95% CI, 0.96–6.09; ref. 16). Another study (17), which included 13 incident cases, showed a nonstatistically significant elevated risk of ovarian cancer associated with impaired fasting glucose or diabetes mellitus (RR = 1.3; 95% CI, 0.71–2.50). In our study, which included more incident cases among women with type II diabetes mellitus than any other prospective cohort study, there were no associations of type II diabetes mellitus status or duration with overall ovarian cancer risk. Though no other study examined diabetes with insulin use in relation to ovarian cancer incidence, our results suggest a possible modest relation. In addition, in this first analysis of type II diabetes mellitus in relation to serous versus nonserous ovarian cancer, an increased risk of nonserous ovarian cancer could not be ruled out.

An association between type II diabetes mellitus (with or without insulin use) and epithelial ovarian cancer is biologically plausible through perturbations in insulin, insulin-like growth factors, gonadotropin, and steroid hormone metabolism, which could affect cell proliferation (23, 24). Consistent with the strong association between type II diabetes mellitus and endometrial cancer risk, it is plausible that type II diabetes mellitus might be more strongly associated with endometrioid/clear cell histologic subtypes (the two most common nonserous epithelial histologic subtypes), but this association was not assessed because of limited power.

The major strengths of this study include the availability of detailed exposure data collected before diagnosis of ovarian cancer from a large cohort of women. The repeated data collection allowed for updating diabetes, insulin use, and oophorectomy status, and thus reduced misclassification over time. The principal limitations include the small number of women ($n = 39$) with type II diabetes mellitus who developed ovarian cancer during follow-up, precluding a more detailed analysis of duration of diabetes or insulin use. In addition, participants might have underreported diabetes status because the disease, especially in early stages, often goes undetected. This underreporting would attenuate associations, as any misclassification is likely to be nondifferential between those who did and did not develop ovarian cancer. Importantly, a previous report from the CPS-II Nutrition cohort showed good agreement between self-reported and medical record data for type II diabetes mellitus in a sample of participants (20). Another limitation is the lack of detailed information on pharmacologic agents used to treat diabetes, such as metformin, which might confound an association between type II diabetes mellitus and risk of ovarian cancer.

In conclusion, results of this study do not support an association of type II diabetes mellitus or duration of diabetes with risk of epithelial ovarian cancer. Larger studies or pooled analyses to improve statistical power are needed to rule out, or identify, possible associations of diabetes with insulin use with epithelial ovarian cancer overall or by histologic subtypes.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: S.M. Gapstur, A.V. Patel, P.T. Campbell
Development of methodology: S.M. Gapstur, W.R. Diver, P.T. Campbell
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): S.M. Gapstur, E.J. Jacobs, P.T. Campbell
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): S.M. Gapstur, A.V. Patel, W.R. Diver, M.M. Gaudet, E.J. Jacobs, P.T. Campbell
Writing, review, and/or revision of the manuscript: S.M. Gapstur, A.V. Patel, W.R. Diver, J.S. Hildebrand, M.M. Gaudet, E.J. Jacobs, P.T. Campbell
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): W.R. Diver, J.S. Hildebrand, P.T. Campbell
Study supervision: S.M. Gapstur

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