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Diabetes Mellitus as a Predictor of Cancer Mortality in a Large Cohort of US Adults

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Several studies have suggested that diabetes mellitus may alter the risk of developing a variety of cancers, and the associations are biologically plausible. To learn more about the relation between diabetes and cancer mortality, the authors examined associations with selected cancers in a large, prospective US cohort of 467,922 men and 588,321 women who had no reported history of cancer at enrollment in 1982. After 16 years of mortality follow-up, diabetes was significantly associated with fatal colon cancer in men (multivariate relative risk (RR) = 1.20, 95% confidence interval (CI): 1.06, 1.37) and women (RR = 1.24, 95% CI: 1.07, 1.43) and with pancreatic cancer in men (RR = 1.48, 95% CI: 1.27, 1.73) and women (RR = 1.44, 95% CI: 1.21, 1.72). For men, diabetes was significantly associated with liver cancer (RR = 2.19, 95% CI: 1.76, 2.72) and bladder cancer (RR = 1.43, 95% CI: 1.14, 1.80). In addition, diabetes was significantly associated with breast cancer in women (RR = 1.27, 95% CI: 1.11, 1.45). These associations were not explained by high body mass. Our findings suggest that diabetes is an independent predictor of mortality from cancer of the colon, pancreas, female breast, and, in men, of the liver and bladder.

breast neoplasms; cohort studies; colonic neoplasms; diabetes mellitus; liver neoplasms; obesity; pancreatic neoplasms; prostatic neoplasms

Abbreviations: BMI, body mass index; CI, confidence interval; IGF-1, insulin-like growth factor 1; RR, relative risk.

An increasing number of epidemiologic studies have found that diabetes mellitus may alter the risk of developing a variety of cancers (1–6). The only consistently observed associations between diabetes and cancer are for pancreatic and liver cancer (2, 3, 5, 6), but relatively few studies of persons with diabetes have examined risk for several cancer sites, and some involved small numbers of diabetics or failed to adjust for important confounding variables (2, 7–10). In addition, the independent contribution of diabetes as a risk factor for cancer, separate from high body mass, has not been adequately defined by prior studies. Further research in this area is important because of the increasing prevalence of obesity in the United States.

Higher insulin levels may contribute to increased tumor growth (11). In recent epidemiologic studies (11–13), insulin-like growth factor 1 (IGF-1) has been associated with increased risk of colorectal cancer. IGF-1 may act as a promoter of colon tumor cell growth. Similar mechanisms may account for associations observed in epidemiologic studies between diabetes and cancer of the breast and other sites. Increases in serum or plasma levels of IGF-1 have been observed in recent epidemiologic studies of prostate and premenopausal breast cancer (14–21). Experimental evidence also suggests that elevated serum IGF-1 levels may be associated with lung cancer, although, to our knowledge, this hypothesis has not yet been examined in epidemiologic studies (12).

Nevertheless, the possible biologic mechanisms are not limited to IGF-1. There may be additional such mechanisms by which diabetes mellitus increases risk of cancer at specific sites. For example, the biologic plausibility of an association between diabetes mellitus and colon cancer may

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also relate to slower bowel transit among diabetics and increased production of carcinogenic bile acids (4). Possible biologic mechanisms for an association between diabetes and liver cancer are less clearly defined (3).

To further evaluate risks of cancer mortality associated with diabetes mellitus, we carried out a study among 467,922 men and 588,321 women who are being followed prospectively as part of the American Cancer Society Cancer Prevention Study II. Study findings regarding diabetes and pancreatic cancer have been published (5), but not for other cancer sites. Although researchers are limited by the lack of laboratory measurements such as IGF-1 levels, the large size of the cohort enables analyses stratified according to level of obesity to examine the separate and joint effects of diabetes and body mass.

The specific aims of the current study were to examine sex-specific associations between diabetes mellitus and cancer mortality for all sites for which sufficient numbers of deaths were available for analysis. Based on prior epidemiologic studies of diabetes and cancer and additional scientific evidence that insulin-like growth factors may have a role in the pathogenesis of certain types of cancer, our a priori hypothesis was that diabetes would be a predictor of mortality from cancer of the female breast, prostate, colon, pancreas, liver, and gallbladder. A further aim was to examine possible effect modification of the associations by weight.

MATERIALS AND METHODS

Study population

The Cancer Prevention Study II is a prospective mortality study of 1.2 million US men and women enrolled in 1982 by more than 77,000 American Cancer Society volunteers in all 50 states, the District of Columbia, and Puerto Rico. Enrollment was restricted to persons aged 30 years or older, where at least one household member was aged 45 years or older. The mean age of the participants at enrollment was 57 years.

Ascertainment of vital status and cancer endpoints

The vital status of the participants was determined by using the National Death Index and by personal inquiries by volunteers (22). Volunteers made personal inquiries in September of 1984, 1986, and 1988 to determine whether their enrollees were alive or deceased and to record the date and place of all deaths. Automated linkage with the National Death Index was used to extend follow-up through December 31, 1998, and to identify deaths of participants lost to follow-up between 1982 and 1988. Death certificates or multiple cause-of-death codes were obtained for 98.8 percent of all participants known to have died. By 1998, 24.0 percent of participants had died, 75.8 percent were still living, and, for 0.2 percent, follow-up was truncated on September 1, 1988, because of insufficient data for National Death Index linkage.

The outcome variables of interest in the present analysis were those specific cancer sites for which there were at least 20 deaths with underlying cause of death (23) for men or women with diabetes (cancer of the esophagus (men only; *International Classification of Diseases*, Ninth Revision, codes 150–150.9), stomach (codes 151–151.9), colon (codes 153–153.9), rectum (codes 154–154.9), liver (codes 155–155.9), gallbladder (codes 156–156.9), pancreas (codes 157–157.9), and lung (codes 162–162.9); melanoma (men only; codes 172–172.9); cancer of the prostate (codes 185–185.9), female breast (codes 174–174.9), endometrium (codes 182–182.9), ovary (codes 183–183.9), bladder (codes 188–188.9), kidney (codes 189–189.9), and brain (codes 191–191.9); non-Hodgkin's lymphoma (codes 202–202.9); multiple myeloma (codes 203–203.9); and leukemia (codes 204–208.9)). We excluded from this analysis participants with a self-reported history of cancer (other than nonmelanoma skin cancer) at enrollment in 1982 (25,239 men and 57,106 women) and those for whom body mass index (BMI; weight in kg/height in m^2) was missing (10,704 men and 14,323 women) or whose BMI was below the range of normal weight (BMI = 18.5; 4,469 men and 16,538 women). After all exclusions, the analytic cohort was comprised of 467,922 men and 588,321 women. Of these, 26,617 men (5.7 percent) and 26,186 women (4.5 percent) reported a history of diabetes. When we analyzed results for pancreatic cancer, deaths that occurred from this cancer within 1 year of baseline (4,380 men, 2,288 women) were excluded because diabetes can occur as an early marker of pancreatic cancer (5). When endometrial cancer was analyzed, we excluded women who reported at baseline that they had had their uterus removed (n = 155,996).

Definition of diabetes and covariates

Participants completed a four-page, baseline, self-administered questionnaire in 1982 that included a section on personal history of disease. They were asked to select the "diseases or conditions for which you have ever been diagnosed by a doctor" from a list that included "diabetes." No information was collected on age at diagnosis or on severity or type of diabetes.

In the baseline questionnaire, information was included on personal identifiers, demographic characteristics, height and weight (1 year before completion of the questionnaire), family history of cancer and other diseases, personal medical history (including history of cancer, colorectal polyps, cirrhosis of the liver, hepatitis, and hypertension), aspirin use, physical activity, cigarette smoking history, and various dietary exposures such as consumption of alcohol and of whole grains and refined grains. For food items such as major types of red meat, fruit, and vegetables, the participants were asked, "On the average, how many days per week do you eat the following foods?" For beverages such as coffee, beer, wine, and hard liquor, they were asked, "How many cups, glasses, or drinks of these beverages do you usually drink a day, and for how many years?" Female respondents were also asked about their use of replacement estrogens and oral contraceptives, age at menarche, parity, age at first livebirth, and menopausal status.

The major covariates of interest included age, gender, race (White, Black, Hispanic, Asian, other), years of education (<high school, high school graduate, some college, college

TABLE 1. Baseline characteristics,*,† by diabetes status, of participants in the American Cancer Society Cancer Prevention Study II, 1982–1998

	Men		Women	
	No diabetes	Diabetes	No diabetes	Diabetes
No. of persons	441,305	26,617	562,135	26,186
No. of person-years	6,358,212	318,168	8,570,637	343,976
Mean age (years) at baseline	57	61	56	61
Education (%)				
<High school	16.4	20.8	14.5	24.7
High school graduate	19.7	21.2	30.4	31.0
Some college	26.9	28.5	30.0	26.8
College graduate	37.0	29.5	25.1	17.6
Smoking status (%)				
Never smoker	25.4	22.6	52.9	54.5
Current cigarette smoker	20.8	20.5	19.9	18.5
Former cigarette smoker	29.4	30.4	20.6	18.5
Ever cigarette, pipe, or cigar smoker	21.4	22.9	1.8	2.3
Race (%)				
White	94.4	88.6	93.1	84.0
Black	3.5	7.8	4.7	12.0
Other	1.7	3.2	1.8	3.4
Body mass index‡ (%)				
18.5–<22.0	8.41	7.7	29.3	14.5
22.0–<25.0	31.0	26.0	32.5	20.7
25.0–<27.0	28.0	23.7	14.5	13.8
27.0–<30.0	22.3	23.3	12.8	19.0
≥30	10.1	19.3	11.0	32.0
Exercise (%)				
None	2.0	3.9	2.1	4.2
Slight	21.5	27.7	23.5	28.4
Moderate	63.5	57.6	66.5	59.3
Heavy	12.0	9.6	5.9	5.7

Table continues

graduate), family history of cancer in a first-degree relative (yes, no), BMI (<22.0, 22.0–<25.0, 25.0–<27.0, 27.0–<30.0, ≥30), physical activity (none, slight, moderate, heavy), cigarette smoking history, alcohol consumption, total red meat consumption, citrus fruit/juice consumption, and vegetable consumption. Cigarette smoking history was characterized as current (at baseline), former, and lifelong nonsmoker; number of cigarettes currently smoked per day (0–19, 20, >20); and duration of cigarette smoking (1–19, 20–29, ≥30 years) by current smokers at study entry. Total red meat consumption (quartiles) was characterized as frequency of intake per week of eight (nonmutually exclusive) items (beef, pork meat, ham, hamburgers, liver, sausages, bacon, and smoked meats). Vegetable consumption (quartiles) was characterized as frequency of intake per week of six items (carrots, tomatoes, squash/corn, green leafy vegetables, raw vegetables, and cabbage, broccoli, and Brussels sprouts).

Use of replacement estrogens (never, current, former) was included as a covariate in all models for women. When looking at predictors of colorectal cancer mortality, we also included history of polyps (yes, no), aspirin use (yes, no), and consumption of whole grains and refined grains (quartiles) as covariates based on purported risk factors for colorectal cancer. History of hepatitis (yes, no) and history of cirrhosis (yes, no) were included as additional covariates when considering predictors of liver cancer mortality. When we looked at predictors of kidney cancer mortality, we also included history of hypertension (yes, no) as a covariate. History of gallstones (yes, no) was included as an additional covariate when looking at predictors of pancreatic cancer mortality. Finally, when considering predictors of mortality from cancer of the breast, ovary, and endometrium, parity (none, 1–2 livebirths, ≥3 livebirths), age at menarche (12, 13, ≥14 years), age at first livebirth (<20, 20–24, 25–29, ≥30 years), and menopausal status (premenopausal, perimenopausal, natural menopause, surgical menopause) were also included as covariates. Oral contraceptive use was also included in the models for ovarian cancer and endometrial cancer.

TABLE 1. Continued

	Men		Women	
	No diabetes	Diabetes	No diabetes	Diabetes
Parity (%)				
Nulliparous			11.4	12.1
1–2 livebirths			37.3	34.5
≥3 livebirths			51.3	53.5
Age (years) at first livebirth (%)				
Nulliparous			11.4	12.1
<20			11.3	17.0
20–24			39.5	37.3
25–29			23.6	19.6
≥30			9.0	7.9
Age (years) at menarche (%)				
≤11			17.4	22.9
12			24.4	24.7
13			27.8	24.5
≥14			26.7	23.7
Menopausal status (%)				
Premenopausal			19.6	15.7
Perimenopausal			7.6	7.3
Postmenopausal			70.4	74.4
ERT§ use (%)				
Never			56.5	54.6
Current			8.9	6.7
Former			17.5	17.6
Unknown			17.2	21.1

* Percentages were directly adjusted to the age distribution of the sex-specific study population.
† Some columns do not add to 100% because of missing data.
‡ Weight in kg/height in m^2.
§ ERT, estrogen replacement therapy.

Statistical analysis

All analyses were carried out separately for men and women. The univariate analyses were adjusted only for age by stratifying by single years of age in a proportional hazards regression model. We used proportional hazards modeling to obtain multivariate estimates of relative risks (hazards ratios) and to adjust for other potential risk factors for fatal cancer (24). Relative risks reported in this paper were obtained from multivariate proportional hazards models, unless otherwise noted.

To thoroughly examine the potential confounding and effect modification by BMI of the association between diabetes and all cancer mortality, we entered interaction terms between diabetes and BMI (<25, 25–<30, and ≥30) into multivariate models, separately by gender and for each cancer site. Using the likelihood ratio test, we assessed statistical significance of the interaction terms at the $p = 0.05$ level (24).

RESULTS

Table 1 shows baseline characteristics of the participants by diabetes status. On average, men and women with a history of diabetes were older, had a lower educational level, had a higher BMI, and were more likely to be Black or physically inactive. On average, women with a history of diabetes had a higher parity, were younger at menarche, and were more likely to be postmenopausal.

Table 2 shows age-adjusted and multivariate relative risks and numbers of deaths from selected cancers among men with diabetes. For men, diabetes was a significant predictor of death from cancer of the colon, liver, pancreas, and bladder. The association with diabetes was strongest for liver cancer (relative risk (RR) = 2.19, 95 percent confidence interval (CI): 1.76, 2.72), pancreatic cancer (RR = 1.48, 95 percent CI: 1.27, 1.73), and bladder cancer (RR = 1.43, 95 percent CI: 1.14, 1.80).

Table 3 shows age-adjusted and multivariate relative risks and numbers of deaths from selected cancers among women with diabetes. For women, diabetes was a significant predictor of death from cancer of the colon, pancreas, and breast, after adjustment for multiple covariates. The association with diabetes was strongest for pancreatic cancer (RR = 1.44, 95 percent CI: 1.21, 1.72). Elevated nonsignificant

TABLE 2. Relation between diabetes and fatal cancer in men, American Cancer Society Cancer Prevention Study II, 1982–1998*

Type of cancer	Diabetics		Nondiabetics		Multivariate RR†	95% CI†
	No. of deaths	Rate‡	No. of deaths	Rate‡		
Esophageal	69	18.1	966	15.5	1.20	0.94, 1.53
Stomach	69	18.7	1,057	17.1	0.99	0.77, 1.27
Colon§	255	67.3	3,272	53.1	1.20	1.06, 1.37
Rectal§	35	9.4	534	8.6	1.07	0.75, 1.51
Liver¶	103	28.1	648	10.5	2.19	1.76, 2.72
Gallbladder	21	5.3	205	3.4	1.46	0.92, 2.30
Pancreas#	184	68.3	1,972	45.1	1.48	1.27, 1.73
Lung	666	179.5	10,638	171.5	1.05	0.97, 1.14
Melanoma	29	7.9	601	9.7	0.93	0.64, 1.36
Prostate	264	66.0	4,421	72.9	0.90	0.80, 1.02
Bladder	83	21.4	913	15.0	1.43	1.14, 1.80
Kidney**	49	14.1	949	15.3	0.82	0.61, 1.10
Brain	49	14.1	958	15.3	0.96	0.72, 1.29
Non-Hodgkin's lymphoma	102	26.9	1,458	23.7	1.21	0.99, 1.48
Multiple myeloma	61	16.0	750	12.2	1.27	0.98, 1.66
Leukemia	84	22.9	1,525	24.8	0.88	0.71, 1.10

* All analyses were adjusted for a core group of covariates (age, race, years of education, body mass index, cigarette smoking history, alcohol consumption, total red meat consumption, consumption of citrus fruits and juices, consumption of vegetables, physical activity). Except for melanoma, non-Hodgkin's lymphoma, and multiple myeloma, analyses for each type of cancer were also adjusted for a family history of that cancer in a first-degree relative.

† RR, relative risk; CI, confidence interval.

‡ Mortality rate per 100,000 age standardized to the Cancer Prevention Study II male population.

§ Also adjusted for polyps, aspirin use, and consumption of whole grains.

¶ Also adjusted for hepatitis and cirrhosis.

Also adjusted for history of gallstones.

** Also adjusted for hypertension.

rates were also observed for cancers of the liver, endometrium, and bladder.

We found little evidence for effect modification by BMI of the observed associations between diabetes and cancer mortality. Significant heterogeneity (p for interaction = 0.04) was observed for lung cancer in men (for BMI categories <25, 25–<30, and ≥30, RR = 0.92 (95 percent CI: 0.81, 1.05), RR = 1.15 (95 percent CI: 1.02, 1.29), and RR = 1.11 (95 percent CI: 0.90, 1.38), respectively). Significant heterogeneity (p for interaction = 0.04) was also observed for pancreatic cancer in women (for BMI categories <25, 25–<30, and ≥30, RR = 1.89 (95 percent CI: 1.45, 2.45), RR = 1.15 (95 percent CI: 0.83, 1.59), and RR = 1.28 (95 percent CI: 0.91, 1.81), respectively). For all other cancer sites, the estimates of risk were not significantly different across levels of BMI.

DISCUSSION

Results from this large prospective mortality study suggest that diabetes may be an independent risk factor for death from cancers of the colon, liver, pancreas, and female breast. For these cancers, we observed higher death rates among diabetics across categories of BMI and (with the exception of breast cancer) for both men and women.

Diabetes was found to be predictive of mortality from colon cancer in the present study. Weak associations with diabetes mellitus have been reported in case-control and cohort studies of colon cancer, although not all have adjusted for other risk factors (4, 25–29). The biologic plausibility of an association between diabetes mellitus and colon cancer relates to slower bowel transit among diabetics (with increased exposure to toxic substances), increased production of carcinogenic bile acids, and higher insulin levels (4). Diabetics also have elevated insulin levels, which have been shown to stimulate IGF-1 in animal studies.

With respect to risk of other cancers among diabetics, several epidemiologic studies have observed an increased risk of primary liver cancer (2, 3, 30–35). The possible biologic mechanisms are poorly understood, but alcohol consumption is a risk factor for both diabetes and liver cancer (3). Although we adjusted for alcohol consumption and other risk factors in the present study, there was likely some residual confounding by factors such as alcohol consumption and history of hepatitis.

TABLE 3. Relation between diabetes and fatal cancer in women, American Cancer Society Cancer Prevention Study II, 1982–1998*

Type of cancer	Diabetics		Nondiabetics		Multivariate RR†	95% CI†
	No. of deaths	Rate‡	No. of deaths	Rate‡		
Stomach	40	10.0	559	6.8	1.25	0.90, 1.73
Colon§	210	50.2	3,027	36.7	1.24	1.07, 1.43
Rectal§	20	5.0	424	5.1	0.90	0.57, 1.42
Liver¶	32	8.0	386	4.7	1.37	0.94, 2.00
Gallbladder	23	5.4	324	3.9	1.19	0.77, 1.83
Pancreas#	137	46.7	1,813	31.0	1.44	1.21, 1.72
Lung	273	70.6	5,952	71.1	1.11	0.98, 1.25
Breast**	240	61.5	4,106	48.8	1.27	1.11, 1.45
Endometrial††	33	12.8	448	7.8	1.33	0.92, 1.90
Ovarian‡‡	73	29.9	1,666	29.1	1.02	0.80, 1.29
Bladder	23	5.2	340	4.2	1.30	0.85, 2.00
Kidney§§	37	9.6	527	6.3	1.12	0.80, 1.58
Brain	38	10.6	850	10.1	1.03	0.74, 1.43
Non-Hodgkin's lymphoma	57	14.2	1,212	14.7	0.93	0.71, 1.21
Multiple myeloma	34	8.2	714	8.6	0.87	0.62, 1.24
Leukemia	59	15.1	1,085	13.2	1.10	0.85, 1.44

* All analyses were adjusted for a core group of covariates (age, race, years of education, body mass index, cigarette smoking history, alcohol consumption, total red meat consumption, consumption of citrus fruits and juices, consumption of vegetables, physical activity, use of replacement estrogens). Except for gallbladder cancer, lung cancer, non-Hodgkin's lymphoma, and multiple myeloma, analyses for each type of cancer were also adjusted for a family history of that cancer in a first-degree relative.

† RR, relative risk; CI, confidence interval.

‡ Mortality rate per 100,000 age standardized to the Cancer Prevention Study II female population.

§ Also adjusted for polyps, aspirin use, and consumption of whole grains.

¶ Also adjusted for hepatitis and cirrhosis.

Also adjusted for history of gallstones.

** Also adjusted for parity, age at menarche, age at first livebirth, and menopausal status.

†† Excludes women who have had a hysterectomy. Also adjusted for parity, age at menarche, age at first livebirth, menopausal status, and oral contraceptive use.

‡‡ Excludes women who have had a hysterectomy or oophorectomy. Also adjusted for parity, age at menarche, age at first livebirth, menopausal status, and oral contraceptive use.

§§ Also adjusted for hypertension.

Studies have also found that diabetics have an increased risk of pancreatic cancer (3, 5, 6, 36, 37). Diabetes is both a risk factor for pancreatic cancer and a potential consequence of pancreatic cancer (36). Abnormal glucose metabolism has also been associated with pancreatic cancer mortality (38, 39). The biologic mechanism by which diabetes may lead to pancreatic cancer relates to hyperinsulinemia (36). Insulin levels are higher in diabetics and in obese persons, and, in recent cohort studies (40, 41), obesity has been associated with pancreatic cancer. Elevated insulin levels may occur early in the natural history of diabetes mellitus and decline over time among diabetics. Experimental studies have shown that insulin promotes growth in human pancreatic cell lines. Peripheral insulin resistance is associated with increased cell turnover of pancreatic islet cells, and stimulation of islet cell proliferation may enhance pancreatic carcinogenesis (36).

Our findings are generally consistent with incidence studies that have found that men with diabetes were less likely to develop prostate cancer (2, 21). The plasma concentration of testosterone, which may be involved in prostate cancer carcinogenesis or progression of the disease, is lower in men with diabetes mellitus (2). Higher testosterone levels have not been consistently associated with prostate cancer risk, however.

Although diabetes was associated with death from female breast cancer in the present study, an association between diabetes mellitus and breast cancer risk in women has not been established by studies carried out to date (2, 7, 9, 33, 42–48). Although results of studies conducted thus far have been inconsistent, the hypothesized association is biologically plausible. Breast cancer has been related to cell proliferation in response to sex hormones and growth factors such as IGF-1 (42). Hyperinsulinemia with insulin resistance has

been reported to be an independent risk factor for breast cancer (49). Circulating insulin levels have been found to be higher in women with premenopausal breast cancer than in age-matched controls with benign breast disease (50).

Epidemiologic studies of a possible association between diabetes mellitus and risk of endometrial cancer have produced inconsistent results (2, 3, 8, 9, 33, 51–58). Other types of cancer associated with diabetes mellitus in prior studies include ovarian cancer (59), cancer of the biliary tract (3), kidney cancer (60–62), and non-Hodgkin's lymphoma (63).

The present study is limited by the lack of laboratory measurements, the use of self-reported information about history of diabetes and other medical conditions, and the lack of information about type of diabetes, duration of diabetes, and age at onset of diabetes. However, in view of the age distribution, most cases of diabetes in this population are likely to be non-insulin-dependent. The lack of cancer incidence data is a further limitation for some sites of cancer less frequently fatal (64, 65). For some rarer cancers and cancers with low fatality rates, the numbers of deaths are modest. In addition, subtypes of cancer (for example, esophageal) cannot be reliably determined from mortality data.

Information obtained from the present study may help to clarify cancer risks for men and women with a history of diabetes mellitus. Whereas the association between diabetes mellitus and pancreatic cancer is fairly well established from studies carried out to date (5, 37), risks of death from cancers at other sites in diabetics are less well understood.

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