Prevalence of Diagnosed Cancer According to Duration of Diagnosed Diabetes and Current Insulin Use Among U.S. Adults With Diagnosed Diabetes

Findings from the 2009 Behavioral Risk Factor Surveillance System

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OBJECTIVE—To estimate the prevalence of diagnosed cancer according to duration of diagnosed diabetes and current insulin use among U.S. adults with diagnosed diabetes.

RESEARCH DESIGN AND METHODS—We analyzed data from 25,964 adults aged ≥18 years with diagnosed diabetes who participated in the 2009 Behavioral Risk Factor Surveillance System.

RESULTS—After adjustment for potential confounders, we found that the greater the duration of diagnosed diabetes, the higher the prevalence of diagnosed cancers ($P < 0.0001$ for linear trend). Among adults with diagnosed type 2 diabetes, the prevalence estimate for cancers of all sites was significantly higher among men (adjusted prevalence ratio 1.6 [95% CI 1.3–1.9]) and women (1.8 [1.5–2.1]) who reported being diagnosed with diabetes ≥15 years ago than among those reporting diabetes diagnosis <15 years ago. The prevalence estimate for cancers of all sites was ~1.3 times higher among type 2 diabetic adults who currently used insulin than among those who did not use insulin among both men (1.3 [1.1–1.6]) and women (1.3 [1.1–1.5]).

CONCLUSIONS—Our results suggest that there is an increased burden of diagnosed cancer among adults with a longer duration of diagnosed diabetes and among type 2 diabetic adults who currently use insulin.

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Growing evidence from epidemiological studies suggests that diabetes is associated with an increased incidence or prevalence of certain types of cancer (1–3). While the exact biological mechanisms linking diabetes and cancer risk are still unknown, it has been proposed that insulin—or insulin-like growth factor, hyperglycemia, insulin resistance, or hyperinsulinemia—and chronic inflammation may play an important role in the diabetes-cancer relationship (1,2).

Duration of diagnosed diabetes may reflect cumulative exposures to diabetes-related underlying causes, medications, complications, and health risk factors. Little is known about the association between duration of diagnosed diabetes and cancer. Furthermore, there is controversy as to whether insulin therapy may increase or decrease cancer risk in people with diabetes. Recent clinical trials have reported positive (4–6), insignificant (7,8), or negative (9) associations between insulin use and risk of cancer in European countries, the U.S., and China. Identifying an association between insulin use and cancer may provide useful insight for both patients and health care providers regarding choice of diabetes medications. To determine whether longer duration of diagnosed diabetes and current insulin use are associated with increased prevalence of cancer among adults with diagnosed diabetes, we analyzed a large population-based sample from the 2009 Behavioral Risk Factor Surveillance System (BRFSS) in the U.S.

RESEARCH DESIGN AND METHODS

The BRFSS is a standardized telephone survey that assesses key behavioral risk factors, lifestyle habits, and chronic illnesses and conditions among adults aged ≥18 years in all U.S. states, District of Columbia, and territories annually. In 2009, the BRFSS collected data using a landline sampling frame, and the median cooperation rate and response rate among states were 75.0 and 52.5%, respectively (10). BRFSS data have consistently been found to provide valid and reliable estimates compared with results from other national household surveys (11).

Assessment of diagnosed diabetes

Diabetes status was ascertained by asking participants, "Have you ever been told by a doctor that you have diabetes?" Responses were coded as "yes," "yes, but female told only during pregnancy," "no," "no, pre-diabetes or borderline diabetes," "don't know/not sure," and "refused." Participants who had an affirmative answer to this question were considered to have diagnosed diabetes; however, gestational diabetes mellitus was coded as "no" diabetes. Thirty-eight states/District of Columbia/U.S. territories collected data on

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diabetes-related information using the Diabetes Module in 2009: Alabama, Alaska, Arizona, Connecticut, Delaware, the District of Columbia, Florida, Georgia, Guam, Illinois, Indiana, Iowa, Kentucky, Louisiana, Massachusetts, Minnesota, Missouri, Montana, Nevada, New Hampshire, New Jersey, New Mexico, North Carolina, North Dakota, Ohio, Pennsylvania, Puerto Rico, South Carolina, Tennessee, Texas, Utah, Vermont, the U.S. Virgin Islands, Virginia, Washington, West Virginia, Wisconsin, and Wyoming. Age at diabetes diagnosis (years) and current insulin use were determined by participants' self-report. Duration of diagnosed diabetes (years) was calculated by subtracting age at diabetes diagnosis from current age. Respondents were classified as having type 1 diabetes if their age at diagnosis was <30 years and they used insulin currently. Persons were classified as having type 2 diabetes if their age at diagnosis was ≥30 years or if their age at diagnosis was <30 years and they did not use insulin currently (12).

Assessment of diagnosed cancer

Cancer status was ascertained by asking participants, "Have you ever been told by a doctor, nurse, or other health professional that you had cancer?" Responses were coded as "yes" or "no." Those responding "yes" were asked the following question: "With your most recent diagnoses of cancer, what type of cancer was it?" A total of 10 major cancer sites/tracts and 29 cancer types were included in the survey: cancer of the breast, the female reproductive tract (cervix, endometrium, and ovary), the male reproductive tract (prostate and testicles), the head/neck (head and neck, oral cavity, pharynx, and thyroid), the gastrointestinal tract (colon, esophagus, liver, pancreas, rectum, and stomach), leukemia/lymphoma (Hodgkin's lymphoma, leukemia, and non-Hodgkin's lymphoma), skin (melanoma and other skin cancer), lungs, the urinary tract (bladder and kidney), and other sites (heart, bone, brain, neuroblastoma, and other). Age at cancer diagnosis was determined by participants' self-report. Participants who had a cancer diagnosis prior to a diabetes diagnosis were excluded from this study.

Assessment of covariates

To examine the potential confounding effects for the association between duration of diagnosed diabetes and cancer, we selected the following variables as covariates: demographic characteristics included sex, age (years), race/ethnicity (non-Hispanic [NH] white, NH black, Hispanic, and NH other), and educational attainment (less than high school, high school, or some college or above). Health insurance coverage at the time of survey (any kind of health care coverage vs. none) was ascertained by participants' self-report.

Smoking status was classified as current smokers (have smoked at least 100 cigarettes during their entire life and smoked in the past month), former smokers (have smoked at least 100 cigarettes during their entire life but did not smoke in the past month), and never smoked. Heavy drinking was defined, for adult men, as consuming on average more than two drinks per day. For adult women, heavy drinking was defined as consuming more than one drink per day. BMI (weight in kilograms divided by the square of height in meters) was calculated by using self-reported weight and height. Obesity was defined as BMI ≥30 kg/m^2 (13). Leisure-time physical activity (any vs. none) was ascertained by asking the question, "During the past month, other than your regular job, did you participate in any physical activity or exercise such as running, calisthenics, golf, gardening, or walking for exercise?" Work-related physical activity was determined by asking employed or self-employed participants, "When you are at work, which of the following best describes what you do? Would you say: 1 = mostly sitting or standing, 2 = mostly walking, and 3 = mostly heavy labor or physically demanding work?" We generated a new variable by combining the employment status and work-related physical activity as follows: 1, employed at a job spent mostly sitting or standing; 2, employed at a job spent mostly walking, performing heavy labor, or doing physically demanding tasks; and 3, not employed (including those who were unemployed, homemakers, students, those who were retired, and those who were unable to work).

Statistical analysis

We reported the demographic characteristics, distribution of behavioral risk factors and lifestyle habits, diabetes-related characteristics, and cancer prevalence according to duration of diagnosed diabetes. Prevalence ratios (PRs) for cancers of all sites were estimated according to duration of diagnosed diabetes adjusting for selected covariates. To account for the possible nonlinear association between duration of diagnosed diabetes and prevalence of cancer, we conducted log linear regression analyses using a cubic spline with four knots at duration of diagnosed diabetes: p5, p25, p75, and p95. The unadjusted prevalence, age-adjusted prevalence, and multiple variable–adjusted prevalence for cancers of all sites were estimated by type of diabetes.

Secondary analyses were conducted among men and women with type 2 diabetes to estimate unadjusted prevalence and adjusted PRs (95% CI) for cancers of all sites and cancer of specific sites/tracts in relation to duration of diagnosed diabetes (<15 vs. ≥15 years) and current insulin use (use vs. no use). The PRs and 95% CIs were estimated using log linear regression models with a robust variance estimator among men and women adjusted for selected covariates.

The linear trends in the means, percentages, or prevalences by duration of diagnosed diabetes in the total sample or differences in prevalences by type of diabetes and current insulin use among men and women with type 2 diabetes were tested by using orthogonal polynomial contrasts. We conducted all analyses using SAS (version 9.2) and SUDAAN software (Release 10.0; Research Triangle Institute, Research Triangle Park, NC). Sample weights were used to account for the varying probabilities of complex sampling design and nonresponse. We considered results with a two-tailed P value <0.05 or an estimate of PR to be significantly different from 1 if the 95% CI did not include 1. The P value of Bonferroni correction for multiple comparisons was set at 0.017 (i.e., 0.05/3).

RESULTS—There were a total of 34,424 adults with diagnosed diabetes participating in the survey with the diabetes module. Of them, 8,460 had missing data on diabetes age, insulin use, and selected covariates. The demographic characteristics of participants in the analytic sample were similar to those with missing data. Among adults with diagnosed diabetes and with complete data on cancer and diabetes-related covariates (n = 25,964), there were 11,165 men (weighted percentage, 52.8%), 18,673 NH whites (65.3%), 3,575 NH blacks (16.0%), 2,348 Hispanics (13.1%), and 1,368 participants with NH other race/ethnicity (5.6%). Approximately 4.7% of adults with diagnosed diabetes were estimated to have type 1 diabetes (n = 491 men and 721 women), 70.5% were type

2 diabetic without current insulin use (n = 7,820 men and 10,475 women), and 24.8% were type 2 diabetic with current insulin use (n = 2,854 men and 3,603 women). The mean age was 58.6 years (median 59.0 years). The mean age at diabetes diagnosis was 47.6 years (49.0 years). The population distribution of age at diabetes diagnosis was approximately symmetric around its median. Among adults with diagnosed diabetes and cancer, the mean age at cancer diagnosis was 61.5 years (61.8 years).

After adjustment for selected covariates, there was an increasing trend in the adjusted PRs for cancers of all sites by duration of diagnosed diabetes among men ($P < 0.0001$ for linear trend) (Fig. 1*A*) and women ($P < 0.0001$ for linear trend) (Fig. 1*B*). The results of spline regression analyses indicated that the adjusted PRs of cancer increased among men with a diabetes diagnosis >1 and <15 years and leveled off or slightly decreased among men with a diabetes diagnosis >15 years compared with those with a diabetes diagnosis <1 year (Fig. 1*C*). Similarly, the adjusted PRs of cancer increased among women with a diabetes diagnosis >1 year and <15 years and leveled off or slightly increased among women with a diabetes diagnosis >15 years (Fig. 1*D*).

The unadjusted prevalence for cancers of all sites among men with type 2 diabetes and current insulin use was higher than those with either type 1 diabetes ($P < 0.001$) or those with type 2 diabetes and no current insulin use ($P < 0.001$) among both men and women (Fig. 2). After adjustment for age, the difference in the prevalence estimates for cancers of all sites remained between adults with type 2 diabetes with current insulin use and those with type 2 diabetes with no current insulin use among men ($P < 0.001$) and women ($P < 0.001$). After adjustment for age and all other selected covariates, the difference in the prevalence estimates

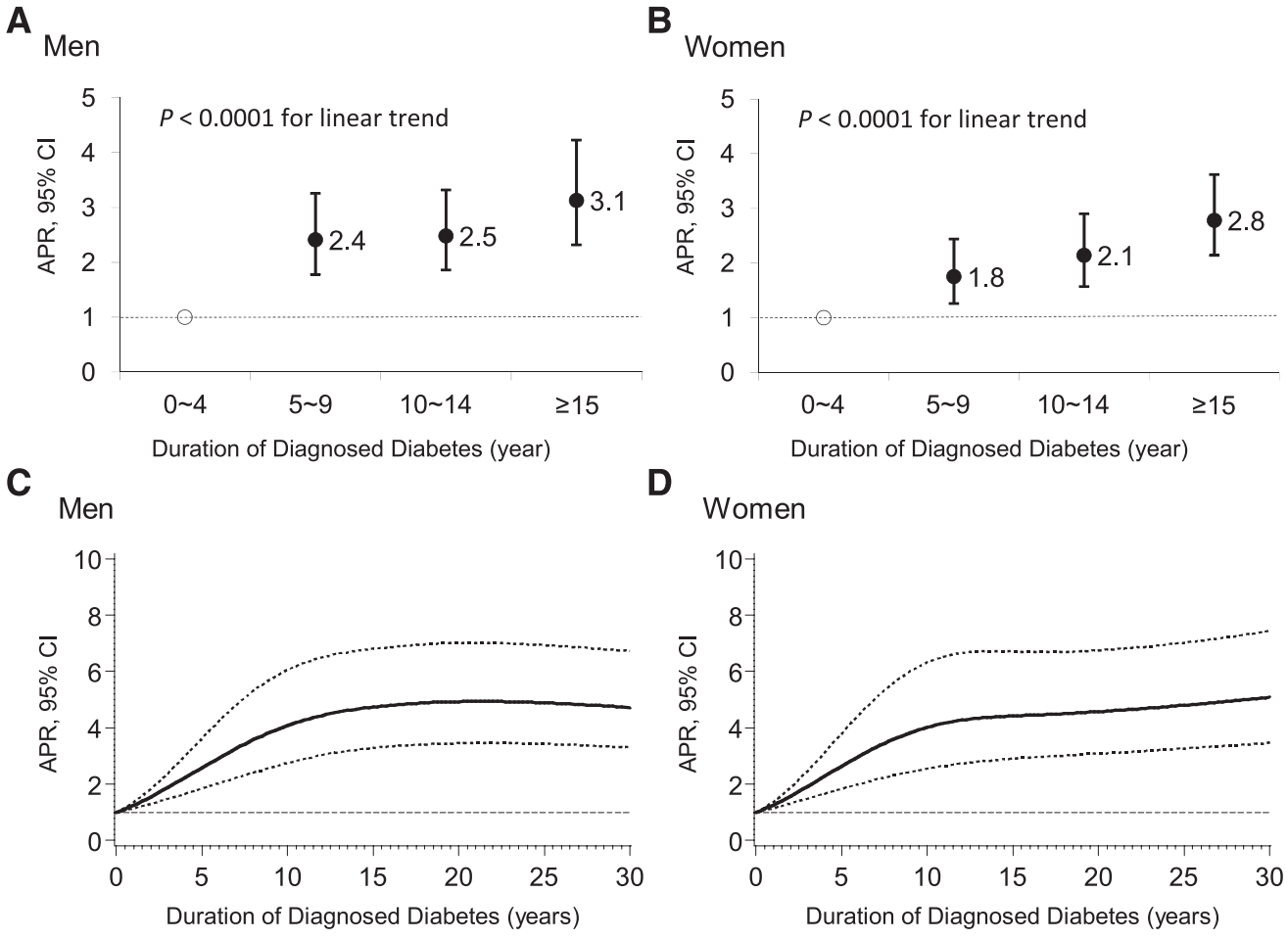

Figure 1—*Adjusted PRs (APRs) of diagnosed cancer in relation to duration of diagnosed diabetes among men* (A *and* C*) and women* (B *and* D*) with diagnosed diabetes (BRFSS 2009).* A *and* B*: Duration of diagnosed diabetes is categorized into 0–4, 5–9, 10–14, and ≥15 years. ●, Point estimates of prevalence ratios; ○, referent groups, which are participants with duration of diagnosed diabetes <1 year. Vertical bars indicate 95% CIs.* C *and* D*: Duration of diagnosed diabetes is in its original continuous scale. Estimates were obtained from log linear regression analyses using a cubic spline with four knots at duration of diagnosed diabetes 0, 3, 15, and 30 years among men and 0, 3, 16, and 33 years among women. Solid lines represent point estimates of PRs. Referent groups are participants with duration of diagnosed diabetes <1 year. Dashed lines indicate 95% CIs. Adjusted for age (continuous, year, centered at mean age of 58 years for men and 59 years for women), age squared, race/ethnicity (NH white, NH black, Hispanic, or NH other), educational attainment (less than high school, high school, or some college or above), health insurance (any vs. none), smoking status (current smoker, former smoker, or never smoked), heavy drinking (yes or no), obesity (yes or no), leisure-time physical activity (any vs. none), a combination of employment status and work-related physical activity (employed at a job spent mostly sitting or standing, employed at a job spent mostly walking or performing heavy labor or doing physically demanding tasks, or not employed), current insulin use (yes or no), and state code.*

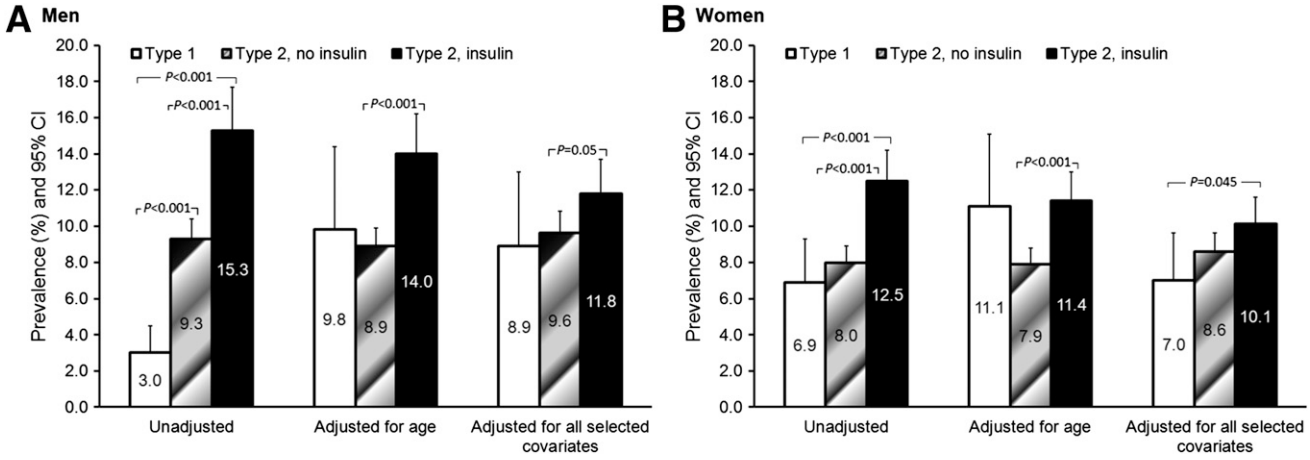

Figure 2—*Unadjusted and adjusted prevalence estimates of self-reported cancer according to diabetes types among men* (A) *and women* (B) *(BRFSS 2009). Prevalence and 95% CIs were adjusted for age (continuous, year, centered at mean age of 58 years for men and 59 years for women), age squared, race/ethnicity (NH white, NH black, Hispanic, or NH other), educational attainment (less than high school, high school, or some college or above), health insurance (any vs. none), smoking status (current smoker, former smoker, or never smoked), heavy drinking (yes vs. no), obesity (yes vs. no), leisure-time physical activity (any vs. none), a combination of employment status and work-related physical activity (employed for a job mostly sitting or standing, employed for a job mostly walking or heavy labor or physically demanding, or not employed), duration of diagnosed diabetes (years), and state code.* P *value of Bonferroni correction for multiple comparisons among diabetes types is set at 0.05/3 = 0.017.*

for diagnosed cancers of all sites among adults with different types of diabetes was attenuated. There was no statistically significant difference in prevalence estimates for diagnosed cancers of all sites across diabetes types (all *P* values >0.017 after Bonferroni correction for multiple comparisons).

Among both men and women with type 2 diabetes, the prevalence estimates for cancers of all sites were significantly higher among those who had diabetes ≥15 years than among those who had diabetes <15 years after adjustment for all selected covariates (Table 1). Specifically, the prevalence was estimated to be significantly higher among adults who had diabetes ≥15 years for colon cancer, melanoma, nonmelanoma skin cancer, and cancer of urinary tract among men and the cancers of the breast, female reproductive tract, and skin among women than those who had diabetes <15 years.

Among both men and women with type 2 diabetes, the prevalence estimate for cancers of all sites was ~1.5 times higher among those who used insulin than those who did not use insulin after adjustment for demographic characteristics and selected health risk factors (model 1 [Table 2]). The associations between current insulin use and cancers of all sites and cancers of specific sites or tracts appear to attenuate after further adjustment for duration of diagnosed diabetes (model 2 [Table 2]). However, current insulin use remained significantly associated with increased prevalence of cancers of all sites among both men and women and increased prevalence of skin cancer (both melanoma and nonmelanoma) among men and cancer of the reproductive tract among women (all *P* values <0.05).

CONCLUSIONS—We used a large population-based sample of U.S. adults with self-reported diagnosed diabetes, and our results indicate that duration of diagnosed diabetes was significantly associated with self-reported cancers of all sites in both men and women. Analyses of adults with type 2 diabetes found an estimated 1.6-fold increased prevalence for cancers of all sites among men ≥15 years after diabetes diagnosis compared with men who had received a diabetes diagnosis within the past 15 years. Similarly, we found an estimated 1.8-fold increased prevalence for cancers of all sites among women with type 2 diabetes who had lived ≥15 years since receiving a diabetes diagnosis compared with women who received a diabetes diagnosis within the past 15 years. We found a 1.3-fold increased prevalence of cancers of all sites among both men and women with type 2 diabetes who currently used insulin compared with those who did not currently use insulin; the association between current insulin use and cancer appeared to be confounded, in part, by duration of diagnosed diabetes.

It is worth commenting on the differences between the findings of prevalence or PRs in our cross-sectional study and that of incidence, incidence rate ratios, or hazard ratios in two recent longitudinal studies (14,15). Carstensen and colleagues (14) and Johnson and colleagues (15) have shown that cancer incidence ratios or hazard ratios are highest among patients within 1 year of diabetes diagnosis and decreasing or leveling off after 2 years of diagnosis compared with persons without diabetes. Those results based on longitudinal data are useful in the assessment of new cancer events and temporal relations between diabetes and cancer (16). In contrast, our results based on cross-sectional data are useful in the assessment of existing cancer state (newly diagnosed, in active treatment, have completed active treatment, and living with progressive symptoms), cancer burden, or cancer survivorship according to duration of diagnosed diabetes and current insulin use. These cross-sectional findings may also be helpful in hypothesis screening for the possible association between diabetes and cancer (16).

Our population-based study focusing on the prevalence estimates of self-reported diagnosed cancer according to duration of diagnosed diabetes may provide additional support for a possible link between diabetes and cancer. Duration of diagnosed diabetes may represent a composite surrogate of the cumulative mixed effects related to underlying causes and treatment

Table 1—*Unadjusted prevalences and adjusted PRs for cancers of all sites according to duration of diagnosed diabetes among men and women with type 2 diabetes*

Cancer type and site/tract	Unadjusted prevalence		*P*	Adjusted PR (95% CI)	
	<15 years	≥15 years		Model 1*	Model 2†
Men (*N* = 10,674)					
All cancers	7.63 (0.46)	21.45 (1.54)	<0.0001	1.7 (1.4–2.0)	1.6 (1.3–1.9)
Breast	0.05 (0.04)‡	0.27 (0.18)‡	NA§	NA	NA
Male reproductive	2.51 (0.32)	7.39 (1.28)	0.0002	1.4 (1.0–2.1)	1.5 (1.0–2.2)
Prostate	2.49 (0.32)	7.27 (1.28)	0.0007	1.4 (1.0–2.1)	1.5 (1.0–2.2)
Head/neck	0.36 (0.11)	0.45 (0.20)‡	NA	NA	NA
Gastrointestinal	0.85 (0.12)	3.23 (0.63)	0.0002	2.4 (1.5–3.7)	2.3 (1.4–3.9)
Colon	0.60 (0.10)	2.68 (0.61)	0.0008	2.8 (1.7–4.7)	2.9 (1.6–5.1)
Leukemia/lymphoma	0.28 (0.12)‡	0.53 (0.20)‡	NA	NA	NA
Skin	2.07 (0.19)	5.94 (0.69)	<0.0001	2.0 (1.5–2.7)	1.6 (1.2–2.2)
Melanoma	0.74 (0.12)	2.17 (0.43)	0.0013	2.2 (1.3–3.6)	1.7 (1.0–2.9)
Other skin cancer	1.33 (0.15)	3.76 (0.55)	<0.0001	1.9 (1.3–2.8)	1.6 (1.1–2.3)
Lung	0.22 (0.07)‡	0.35 (0.11)‡	NA	NA	NA
Urinary	0.42 (0.09)	1.50 (0.41)	0.01	2.6 (1.3–5.0)	2.4 (1.1–5.2)
Other	0.79 (0.15)	1.12 (0.27)	0.29	1.0 (0.6–1.9)	1.1 (0.6–2.2)
Women (*N* = 14,078)					
All cancers	6.69 (0.44)	15.58 (0.94)	<0.0001	1.9 (1.6–2.2)	1.8 (1.5–2.1)
Breast	1.88 (0.20)	5.32 (0.58)	<0.0001	2.0 (1.5–2.8)	2.0 (1.5–2.8)
Female reproductive	1.05 (0.26)	1.89 (0.37)	0.062	2.5 (1.6–4.1)	2.3 (1.4–3.8)
Head/neck	0.24 (0.06)	0.32 (0.10)	0.46	1.1 (0.5–2.2)	1.0 (0.4–2.5)
Gastrointestinal	0.85 (0.17)	1.46 (0.26)	0.049	1.5 (0.9–2.6)	1.4 (0.8–2.3)
Colon	0.63 (0.14)	1.12 (0.22)	0.063	1.5 (0.8–2.8)	1.4 (0.8–2.4)
Leukemia/lymphoma	0.28 (0.10)‡	0.48 (0.18)	NA	NA	NA
Skin	1.38 (0.17)	4.14 (0.57)	<0.0001	2.2 (1.6–3.1)	2.2 (1.5–3.3)
Melanoma	0.48 (0.12)	1.17 (0.38)	0.084	1.7 (0.9–3.4)	1.7 (0.8–3.5)
Other skin cancer	0.90 (0.12)	2.98 (0.43)	<0.0001	2.5 (1.7–3.6)	2.5 (1.6–3.9)
Lung	0.16 (0.04)	0.21 (0.11)‡	NA	NA	NA
Urinary	0.16 (0.04)	0.32 (0.09)	0.13	1.5 (0.7–3.2)	1.2 (0.5–2.7)
Other	0.57 (0.13)	1.01 (0.23)	0.096	1.3 (0.7–2.5)	1.1 (0.6–2.2)

Data are percent (SE) unless otherwise indicated. Data are from BRFSS 2009 (10). *Adjusted for age (continuous, year, centered at mean age of 58 years for men and 59 years for women), age squared, race/ethnicity (NH white, NH black, Hispanic, or NH other), educational attainment (less than high school, high school, or some college or above), health insurance (any or none), smoking status (current smoker, former smoker, or never smoked), heavy drinking (yes or no), obesity (yes or no), leisure-time physical activity (any or none), a combination of employment status and work-related physical activity (employed at a job spent mostly sitting or standing, employed at a job spent mostly walking or performing heavy labor or doing physically demanding tasks, or not employed), and state code. †Adjusted for all covariates in model 1 and current insulin use. ‡Does not meet the standard of statistical reliability and precision (i.e., relative SE >30%). §Estimates are not shown owing to lack of statistical precision.

of diabetes and exposures to environmental hazards and health risk factors. A recent study has shown that diabetes duration is related to ~40% increased risk of all-cause mortality among diabetic men aged 60–79 years (17). The significant dose-response relationship between duration of diagnosed diabetes and cancer prevalence as shown in our study suggests that long-term exposure to diabetes-specific factors (e.g., hyperglycemia or HbA_{1c} levels, insulin resistance, use of antidiabetes medications, health and behavioral risk factors, worsening lipid and lipoprotein profiles, and chronic complications) and possible synergistic effects among these factors may provide further support for the association between diabetes and cancer (1,2). In addition, it is possible that certain environmental factors (e.g., pesticides) may be related to both diabetes and cancer (18,19). Moreover, findings of animal studies suggest some possible genetic links between type 2 diabetes and cancer (20).

Although studies have shown that people with type 1 diabetes have increased incidence for cancers of the pancreas, stomach, cervix, endometrium, skin, and leukemia (21,22), relatively little is known about the association of type 1 diabetes with cancer compared with type 2 diabetes. The higher prevalence of cancer among people with type 2 diabetes, particularly those who use insulin, compared with those with type 1 diabetes suggests that insulin resistance and unhealthy lifestyle habits may play a role in these associations (23). There are distinct etiologies and some differences in lifestyle factors between persons with type 1 and type 2 diabetes (24). Further research may be warranted on the association between diabetes types and cancer, since persons with type 1 diabetes and persons with type 2 diabetes share many similarities in clinical manifestations, medical treatment, and health outcomes despite differences in the etiology and lifestyle factors (24).

Previous meta-analyses have shown that the risk of colorectal cancer is ~30% higher and the risk of bladder cancer is ~24% higher in people with diabetes than those without diabetes (25,26). Our

Table 2—*Unadjusted prevalences and adjusted PRs for cancers of all sites according to current insulin use status among men and women with type 2 diabetes*

	Unadjusted prevalence			Adjusted PR (95% CI)	
Cancer type and site/tract	Insulin use	No insulin use	*P*	Model 1*	Model 2†
Men (*N* = 10,674)					
All cancers	15.28 (1.21)	9.31 (0.57)	<0.0001	1.5 (1.2–1.8)	1.3 (1.1–1.6)
Breast	0.38 (0.20)‡	Rare§	NA‖	NA	NA
Male reproductive	4.07 (0.82)	3.49 (0.44)	0.54	1.0 (0.7–1.6)	0.9 (0.6–1.4)
Prostate	4.93 (0.82)	3.48 (0.44)	0.63	1.0 (0.6–1.5)	0.9 (0.5–1.5)
Head/neck	0.68 (0.30)‡	0.28 (0.08)	NA	NA	NA
Gastrointestinal	1.92 (0.33)	1.22 (0.21)	0.071	1.4 (0.8–2.3)	1.1 (0.6–1.9)
Colon	1.31 (0.25)	1.00 (0.20)	0.35	1.2 (0.6–2.1)	0.9 (0.5–1.6)
Leukemia/lymphoma	0.63 (0.33)‡	0.23 (0.07)‡	NA	NA	NA
Skin	4.98 (0.64)	2.27 (0.19)	0.0001	2.2 (1.7–3.0)	1.9 (1.4–2.6)
Melanoma	1.93 (0.41)	0.78 (0.11)	0.007	2.5 (1.5–4.0)	2.1 (1.2–3.5)
Other skin cancer	3.05 (0.49)	1.50 (0.16)	0.0027	2.1 (1.4–3.1)	1.8 (1.3–2.7)
Lung	0.50 (0.18)‡	0.16 (0.05)‡	NA	NA	NA
Urinary	1.04 (0.31)	0.55 (0.12)	0.14	1.6 (0.7–3.6)	1.3 (0.5–3.0)
Other sites	0.80 (0.25)	0.89 (0.16)	0.75	0.8 (0.4–1.5)	0.7 (0.4–1.6)
Women (*N* = 14,078)					
All cancers	12.49 (0.86)	7.96 (0.47)	<0.0001	1.5 (1.3–1.8)	1.3 (1.1–1.5)
Breast	3.61 (0.44)	2.53 (0.25)	0.032	1.2 (0.9–1.7)	1.0 (0.7–1.4)
Female reproductive	1.78 (0.43)	1.12 (0.25)	0.18	2.0 (1.2–3.6)	1.7 (1.0–3.2)
Head/neck	0.38 (0.13)‡	0.22 (0.06)	NA	NA	NA
Gastrointestinal	1.51 (0.28)	0.86 (0.17)	0.048	1.7 (1.0–2.8)	1.6 (0.9–2.6)
Colon	1.18 (0.24)	0.63 (0.14)	0.048	1.7 (1.0–3.0)	1.6 (0.9–2.6)
Leukemia/lymphoma	0.39 (0.15)‡	0.32 (0.09)	NA	NA	NA
Skin	2.59 (0.41)	1.95 (0.22)	0.17	1.3 (0.9–1.9)	1.0 (0.7–1.5)
Melanoma	0.79 (0.25)	0.62 (0.16)	0.56	1.4 (0.7–2.8)	1.2 (0.5–2.6)
Other skin cancer	1.80 (0.33)	1.33 (0.16)	0.20	1.3 (0.8–1.9)	1.0 (0.6–1.6)
Lung	0.28 (0.12)‡	0.14 (0.04)	NA	NA	NA
Urinary	0.39 (0.12)	0.15 (0.04)	NA	2.2 (1.0–4.9)	2.1 (0.9–4.9)
Other sites	1.18 (0.28)	0.54 (0.12)	0.034	1.8 (1.0–3.3)	1.8 (1.0–3.2)

Data are percent (SE) unless otherwise indicated. Data are from BRFSS 2009 (10). *Adjusted for age (continuous, year, centered at mean age of 58 years for men and 59 years for women), age squared, race/ethnicity (NH white, NH black, Hispanic, and other), educational attainment (less than high school, high school, or some college or above), health insurance (any or none), smoking status (current smoker, former smoker, and never smoked), heavy drinking (yes or no), obesity (yes or no), leisure-time physical activity (any or none), a combination of employment status and work-related physical activity (employed at a job spent mostly sitting or standing, employed at a job spent mostly walking or performing heavy labor or doing physically demanding tasks, or not employed), and state code. †Adjusted for all covariates in model 1 and duration of diagnosed diabetes. ‡Does not meet the standard of statistical reliability and precision (i.e., relative SE >30%). §Rare, i.e., prevalence estimate is between 0 and 0.01%. ‖Estimates are not shown owing to lack of statistical precision.

results provide insight into the association between duration of diagnosed diabetes and diagnosed cancer in type 2 diabetes such that men who had type 2 diabetes diagnosis for ≥15 years had more than threefold higher prevalence for colon cancer and nearly threefold higher prevalence for cancer of urinary tract (including both bladder and kidney) than men who had type 2 diabetes diagnosis <15 years. However, the association between duration of diagnosed diabetes and cancers of the colon and the urinary tract was weak among women with type 2 diabetes. It is unknown why the association between duration of diagnosed diabetes and colon cancer and urinary tract cancer prevalence differed between men and women; however, previous studies have suggested that there are differences between men and women in colon cancer and bladder cancer survival and health-related risk factors (27–31), which may in part contribute to the sex differences in the association between duration of diagnosed diabetes and cancers of the colon and urinary tract.

As shown in meta-analyses (32), there is ~20% increased risk of breast cancer and a nearly twofold increased risk of endometrial cancer among women with diabetes compared with women without diabetes. Our results provide insight by showing an approximately twofold higher prevalence of cancers of the breast and the reproductive tract among women ≥15 years post–diagnosis of type 2 diabetes compared with women still in the first 15 years since type 2 diabetes diagnosis. These results support the notion that exposure to a high circulating concentration of insulin might result in mitogenic effects on breast tissue that stimulate the growth of endometrial stromal cells (33,34).

One of the unique findings in our study was the strong association of duration of diagnosed diabetes with skin cancer among men and women with type 2 diabetes. A previous study on patients hospitalized for type 1 diabetes in Sweden noted a fivefold increased risk of squamous cell skin cancer among persons with type 1 diabetes compared with those without diabetes (22). A recent study reported a

risk of malignant melanoma in persons with diabetes compared with those without the disease (35). Clinical studies have shown that cutaneous manifestations are common among people with diabetes (36). Future research is warranted to determine whether there are biological mechanisms linking cutaneous manifestations of diabetes and development of skin cancers or whether the cutaneous manifestations of diabetes increase the probabilities of early clinical detections for skin cancers.

Inconsistent findings on the association between insulin use and risk of cancer in type 2 diabetes have been reported in recent clinical trials (4,5,7–9). A German cohort study suggested a dose-response relation such that those taking higher doses of insulin glargine (Lantus) had an increased risk for cancer incidence compared with those prescribed human insulin and that both insulin glargine and human insulin were related to an increased risk of cancer incidence and mortality (4). A U.K. study suggested that insulin-based regimens may be associated with ~40% higher risk of all cancers, 70% higher risk of colorectal cancer, and fivefold higher risk of pancreatic cancer compared with metformin monotherapy (5). Swedish and Scottish studies did not detect a significant association between insulin glargine alone or insulin glargine in combination with other insulin and cancer incidence compared with treatment with nonglargine insulin (7,8). In contrast, researchers reported that insulin use was associated with reduced cancer risk among Chinese patients with type 2 diabetes (9). Our results showing ~30% elevated cancer prevalence in both men and women who were currently treated with insulin compared with those who were not currently treated with insulin, even after adjustment for duration of diagnosed diabetes, are similar to some findings from previous studies and suggest a need for further research into a possible link between insulin use, particularly insulin analogs, and increased risk of cancer.

The major strength of our study was the use of a large population-based sample, which enabled us to provide stable estimates of cancer prevalence among adults with diabetes in the general population. There were also several limitations. First, in this cross-sectional study persons who self-reported diagnosed cancer were cancer survivors and included those who were newly diagnosed and those who had a preexisting condition. Persons who died of cancer were excluded in this self-reported cross-sectional survey. Therefore, these results based on the prevalence of diagnosed cancer suggest cross-sectional associations and preclude causal associations between duration of diagnosed diabetes or current insulin use and cancer. Available information on the age at diabetes diagnosis and age at cancer diagnosis in our study was useful for identifying participants who had cancer prior to diabetes and, hence, excluding them from the analyses. Second, diagnosed diabetes, age at diagnosis of diabetes or cancer, current insulin use, and cancer types were self-reported by survey participants; thus, recall bias may be possible. Although there is substantial agreement in the determinations of diabetes and cancer status based on self-reports and physician diagnoses (37,38), misclassification bias of the diabetes and cancer status could have resulted in the underestimation of our results. Third, duration of diagnosed diabetes may not represent actual duration of exposure to diabetes because people may be asymptomatic for many years before medical diagnosis. Indeed, ~27% of people with diabetes are undiagnosed (39). In addition, recall bias on duration of diagnosed diabetes may also be possible because persons with a recent diagnosis of diabetes probably remembered the year of diagnosis better than those with an earlier diagnosis. Fourth, information on the type, dosage, and duration of using insulin and other medications (e.g., oral agents) was unavailable in our data; therefore, we were unable to identify their possible confounding effects for the associations between insulin use and cancer prevalence. Drug use indication bias and prevalent user bias may be possible when assessing these associations using cross-sectional health survey data (40). Fifth, because weight, height, smoking, drinking, and physical activity were also self-reported by participants at the time of interview, they may not reflect the status at the time when diabetes or cancer was diagnosed and may be subject to possible social desirability bias. Sixth, the BRFSS survey excludes adults who have been institutionalized or are hospitalized and those with only mobile telephones. Because these adults are more likely to be of low socioeconomic status or to have severe physical or mental illness, this exclusion may have led us to underestimate the true prevalence of cancer among U.S. adults with diabetes. Approximately one-fourth of adults with diagnosed diabetes had missing data, which may potentially introduce bias to our estimates. Since subpopulation analyses (or domain analyses) take the variability due to missing data into account by using the entire sample in estimating the variance of domain estimates, this bias could be minimal.

In conclusion, using data from a large population-based survey we found that duration of diagnosed diabetes was significantly and positively associated with the prevalence of cancers of all sites and of some specific sites. Furthermore, current insulin use was also significantly associated with elevated prevalence of cancers of all sites and some specific sites. These findings provide support for a possible relationship between diabetes and cancer. While our cross-sectional results provide useful information for an association between duration of diagnosed diabetes or current insulin use and cancer prevalence, further clinical research with a longitudinal design is warranted to confirm a possible causal link between diabetes and cancer.

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C.L. developed the study concept and design, acquired data, analyzed and interpreted data, provided statistical analyses, and wrote the manuscript. G.Z., C.A.O., and X.-J.W. developed the study concept and design, interpreted data, and reviewed and edited the manuscript. E.S.F. and L.S.B. developed the study concept and design, interpreted data, reviewed and edited the manuscript, and supervised the study. C.L. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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References

1. Giovannucci E, Harlan DM, Archer MC, et al. Diabetes and cancer: a consensus report. CA Cancer J Clin 2010;60:207–221
2. Richardson LC, Pollack LA. Therapy insight: Influence of type 2 diabetes on the development, treatment and outcomes of cancer. Nat Clin Pract Oncol 2005;2:48–53
3. Li C, Balluz LS, Ford ES, Okoro CA, Tsai J, Zhao G. Association between diagnosed diabetes and self-reported cancer among U.S. adults: findings from the 2009 Behavioral Risk Factor Surveillance System. Diabetes Care 2011;34:1365–1368

4. Hemkens LG, Grouven U, Bender R, et al. Risk of malignancies in patients with diabetes treated with human insulin or insulin analogues: a cohort study. Diabetologia 2009;52:1732–1744
5. Currie CJ, Poole CD, Gale EA. The influence of glucose-lowering therapies on cancer risk in type 2 diabetes. Diabetologia 2009;52:1766–1777
6. Vinikoor LC, Long MD, Keku TO, Martin CF, Galanko JA, Sandler RS. The association between diabetes, insulin use, and colorectal cancer among Whites and African Americans. Cancer Epidemiol Biomarkers Prev 2009;18:1239–1242
7. Jonasson JM, Ljung R, Talbäck M, Haglund B, Gudbjörnsdòttir S, Steineck G. Insulin glargine use and short-term incidence of malignancies-a population-based follow-up study in Sweden. Diabetologia 2009;52:1745–1754
8. Colhoun HM; SDRN Epidemiology Group. Use of insulin glargine and cancer incidence in Scotland: a study from the Scottish Diabetes Research Network Epidemiology Group. Diabetologia 2009;52:1755–1765
9. Yang X, Ko GT, So WY, et al. Associations of hyperglycemia and insulin usage with the risk of cancer in type 2 diabetes: the Hong Kong diabetes registry. Diabetes 2010;59:1254–1260
10. Centers for Disease Control and Prevention. Behavioral Risk Factor Surveillance System: technical information and 2009 survey data [article online]. 2012. Available from http://www.cdc.gov/brfss/technical_infodata/surveydata/2009.htm. Accessed 1 August 2010
11. Li C, Balluz LS, Ford ES, Okoro CA, Zhao G, Pierannunzi C. A comparison of prevalence estimates for selected health indicators and chronic diseases or conditions from the Behavioral Risk Factor Surveillance System, the National Health Interview Survey, and the National Health and Nutrition Examination Survey, 2007-2008. Prev Med 2012;54:381–387
12. World Health Organization Study Group. Prevention of Diabetes. Geneva, World Health Org., 1994
13. World Health Organization. *Physical Status: the Use and Interpretation of Anthropometry: Report of a WHO Expert Committee*. Geneva, World Health Org., 1995 (*Tech. Rep. Ser., no. 854*)
14. Carstensen B, Witte DR, Friis S. Cancer occurrence in Danish diabetic patients: duration and insulin effects. Diabetologia 2012;55:948–958
15. Johnson JA, Bowker SL, Richardson K, Marra CA. Time-varying incidence of cancer after the onset of type 2 diabetes: evidence of potential detection bias. Diabetologia 2011;54:2263–2271
16. Rothman KJ, Greenland S, Lash TL. Modern Epidemiology. Philadelphia, Lippincott Williams & Wilkins, 2008
17. Wannamethee SG, Shaper AG, Whincup PH, Lennon L, Sattar N. Impact of diabetes on cardiovascular disease risk and all-cause mortality in older men: influence of age at onset, diabetes duration, and established and novel risk factors. Arch Intern Med 2011;171:404–410
18. Jaga K, Dharmani C. The epidemiology of pesticide exposure and cancer: A review. Rev Environ Health 2005;20:15–38
19. Lee DH, Lind PM, Jacobs DR Jr, Salihovic S, van Bavel B, Lind L. Polychlorinated biphenyls and organochlorine pesticides in plasma predict development of type 2 diabetes in the elderly: the prospective investigation of the vasculature in Uppsala Seniors (PIVUS) study. Diabetes Care 2011;34:1778–1784
20. Zhu H, Shyh-Chang N, Segrè AV, et al.; DIAGRAM Consortium; MAGIC Investigators. The Lin28/let-7 axis regulates glucose metabolism. Cell 2011;147:81–94
21. Zendehdel K, Nyrén O, Ostenson CG, Adami HO, Ekbom A, Ye W. Cancer incidence in patients with type 1 diabetes mellitus: a population-based cohort study in Sweden. J Natl Cancer Inst 2003;95:1797–1800
22. Shu X, Ji J, Li X, Sundquist J, Sundquist K, Hemminki K. Cancer risk among patients hospitalized for Type 1 diabetes mellitus: a population-based cohort study in Sweden. Diabet Med 2010;27:791–797
23. Godsland IF. Insulin resistance and hyperinsulinaemia in the development and progression of cancer. Clin Sci (Lond) 2010;118:315–332
24. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2011;34(Suppl. 1):S62–S69
25. Larsson SC, Orsini N, Wolk A. Diabetes mellitus and risk of colorectal cancer: a meta-analysis. J Natl Cancer Inst 2005;97:1679–1687
26. Larsson SC, Orsini N, Brismar K, Wolk A. Diabetes mellitus and risk of bladder cancer: a meta-analysis. Diabetologia 2006;49:2819–2823
27. Li C, Ford ES, McGuire LC, Mokdad AH, Little RR, Reaven GM. Trends in hyperinsulinemia among nondiabetic adults in the U.S. Diabetes Care 2006;29:2396–2402
28. Paulson EC, Wirtalla C, Armstrong K, Mahmoud NN. Gender influences treatment and survival in colorectal cancer surgery. Dis Colon Rectum 2009;52:1982–1991
29. Wichmann MW, Müller C, Hornung HM, Lau-Werner U, Schildberg FW; Colorectal Cancer Study Group. Gender differences in long-term survival of patients with colorectal cancer. Br J Surg 2001;88:1092–1098
30. Scosyrev E, Noyes K, Feng C, Messing E. Sex and racial differences in bladder cancer presentation and mortality in the US. Cancer 2009;115:68–74
31. Shariat SF, Sfakianos JP, Droller MJ, Karakiewicz PI, Meryn S, Bochner BH. The effect of age and gender on bladder cancer: a critical review of the literature. BJU Int 2010;105:300–308
32. Larsson SC, Mantzoros CS, Wolk A. Diabetes mellitus and risk of breast cancer: a meta-analysis. Int J Cancer 2007;121:856–862
33. Chappell J, Leitner JW, Solomon S, Golovchenko I, Goalstone ML, Draznin B. Effect of insulin on cell cycle progression in MCF-7 breast cancer cells. Direct and potentiating influence. J Biol Chem 2001;276:38023–38028
34. Nagamani M, Stuart CA. Specific binding and growth-promoting activity of insulin in endometrial cancer cells in culture. Am J Obstet Gynecol 1998;179:6–12
35. Chodick G, Heymann AD, Rosenmann L, et al. Diabetes and risk of incident cancer: a large population-based cohort study in Israel. Cancer Causes Control 2010;21:879–887
36. Behm B, Schreml S, Landthaler M, Babilas P. Skin signs in diabetes mellitus. J Eur Acad Dermatol Venereol 2012;26:1203–1211
37. Bowlin SJ, Morrill BD, Nafziger AN, Jenkins PL, Lewis C, Pearson TA. Validity of cardiovascular disease risk factors assessed by telephone survey: the Behavioral Risk Factor Survey. J Clin Epidemiol 1993;46:561–571
38. Desai MM, Bruce ML, Desai RA, Druss BG. Validity of self-reported cancer history: a comparison of health interview data and cancer registry records. Am J Epidemiol 2001;153:299–306
39. Centers for Disease Control and Prevention. National diabetes fact sheet: national estimates and general information on diabetes and prediabetes in the United States, 2011. Atlanta, GA, U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, 2011
40. Yang XL, Ma RC, So WY, Kong AP, Xu G, Chan JC. Addressing different biases in analysing drug use on cancer risk in diabetes in non-clinical trial settings—what, why and how? Diabetes Obes Metab 2012;14:579–585