Association Between Diagnosed Diabetes and Self-Reported Cancer Among U.S. Adults

Findings from the 2009 Behavioral Risk Factor Surveillance System

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OBJECTIVE—To assess the association between diagnosed diabetes and self-reported cancer among U.S. adults.

RESEARCH DESIGN AND METHODS—We analyzed data for 397,783 adults who participated in the 2009 Behavioral Risk Factor Surveillance System and had valid data on diabetes and cancer.

RESULTS—After adjustment for potential confounders, diabetic men had higher adjusted prevalence ratios for cancers of the prostate (1.1 [95% CI 1.0–1.3]), colon (1.3 [1.0–1.7]), pancreas (4.6 [1.8–11.7]), rectum (2.2 [1.0–4.7]), urinary bladder (1.7 [1.2–2.2]), and kidney (1.9 [1.2–3.0]) than nondiabetic men (all P < 0.05). Diabetic women had higher adjusted prevalence ratios for cancers of the breast (1.1 [1.0–1.3]) and endometrium (1.6 [1.2–2.0]), and leukemia (2.3 [1.3–4.2]) than nondiabetic women (all P < 0.05).

CONCLUSIONS—Our results suggest that diabetic adults have higher prevalences of certain cancers than nondiabetic adults.

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iabetes and cancer are two common chronic diseases that exert serious adverse effects on public health in the U.S. Approximately 25.6 million adults (11.3%) aged 20 years or older were estimated to have diabetes in 2010 (1). Approximately 11.7 million Americans were living with cancer in 2007. Studies have found that diabetes is associated with an increased risk for certain types of cancer (2,3), and diabetes may increase the risk of all-cause mortality among people with cancer (4). To compare the prevalence of cancer between adults without and with diabetes, we analyzed a large populationbased sample from the Centers for Disease

Control and Prevention 2009 Behavioral Risk Factor Surveillance System (BRFSS) in the U.S.

RESEARCH DESIGN AND

METHODS—The BRFSS is a standardized telephone survey that annually assesses key behavioral risk factors and chronic diseases among adults aged 18 years or older in all U.S. states, District of Columbia, and territories. The median cooperation rate among states was 75.0% in 2009 (5). BRFSS data have consistently provided valid and reliable estimates compared with national household surveys (6,7).

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," or "no." Gestational diabetes was coded as "no" diabetes.

Cancer status was ascertained by asking participants, "Have you ever been told by a doctor, nurse, or other health professional that you have cancer?" Responses were coded as "yes," or "no." For those who answered "yes" to this question, the following questions were asked, "With your most recent diagnoses of cancer, what type of cancer was it?" The survey included 10 major cancer sites/tracts and 29 cancer types: breast cancer, male reproductive tract (prostate cancer, testicular cancer), head/neck (head and neck cancer, oral cancer, pharyngeal cancer, thyroid cancer), gastrointestinal tract (colon cancer, esophageal cancer, liver cancer, pancreatic cancer, rectal cancer, stomach cancer), leukemia/lymphoma (Hodgkin's lymphoma, leukemia, non-Hodgkin's lymphoma), skin (melanoma, other skin cancer), lung cancer, urinary tract (urinary bladder cancer, kidney cancer), and other sites (heart cancer, bone cancer, brain cancer, neuroblastoma, other).

Demographic characteristics included sex, age (year), and race/ethnicity (non–Hispanic white, non–Hispanic black, Hispanic, and other). Healthrelated risk factors included health insurance coverage (none vs. any type of health insurance), smoking status (current smoker, former smoker, and never smoked), heavy drinking (consuming more than two drinks per day among men and more than one drink per day among women), BMI (kg/m²), and physical inactivity.

We estimated the crude prevalence for cancer of all sites and specific types of cancer according to diabetes status. We estimated the prevalence ratios and their 95% CIs using log-linear models with a robust error variance estimator (8). The

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Diabetes and cancer among U.S. adults

Table 1-Prevalences and prevalence ratios of cancer according to diabetes status among men and women, BRFSS 2009

		Crude prevalence, % (SE)			Prevalence ratio (95% CI)		
Cancer site/tract	Cancer type	Diabetes	No diabetes	Р	Model 1*	Model 2†	Model 3‡
Men, N		19,719	131,740				
,	All cancers	15.89 (0.45)	7.49 (0.11)	< 0.0001	2.1 (2.0–2.3)	1.1 (1.0–1.1)	1.1 (1.1–1.2)
Breast cancer		0.10 (0.04)	0.02 (0.01)	0.029	5.2 (2.1–12.7)	3.0 (1.2–7.1)	1.5 (0.4–4.8)
Male reproductive		5.35 (0.31)	2.06 (0.06)	< 0.0001	2.6 (2.3–3.0)	1.1 (1.0–1.3)	1.1 (1.0–1.3)
	Prostate	5.11 (0.31)	1.89 (0.05)	< 0.0001	2.7 (2.4–3.1)	1.2 (1.0–1.3)	1.1 (1.0–1.3)
	Testicular	0.27 (0.06)	0.18 (0.03)	0.20	1.5 (0.9–2.5)	1.2 (0.7–2.1)	1.1 (0.5–2.2)
Head/neck		0.58 (0.09)	0.27 (0.02)	0.0006	2.2 (1.6–3.1)	1.2 (0.8–1.6)	1.2 (0.8–1.7)
	Head and neck	0.11 (0.04)	0.06 (0.01)	0.18	1.9 (0.9–3.8)	1.0 (0.5–2.0)	1.2 (0.6–2.5)
	Oral	0.07 (0.03)	0.05 (0.01)	0.43	1.5 (0.6–3.4)	0.9 (0.4–1.8)	0.9 (0.4–2.1)
	Pharyngeal	0.14 (0.04)	0.06 (0.01)	0.066	2.2 (1.2-4.2)	1.0 (0.5–1.9)	1.0 (0.5–1.9)
	Thyroid	0.26 (0.07)	0.10 (0.01)	0.014	2.7 (1.5-4.8)	1.6 (0.9–2.8)	1.4 (0.8–2.6)
Gastrointestinal	,	1.90 (0.17)	0.58 (0.03)	< 0.0001	3.2 (2.7-4.0)	1.5 (1.2–1.8)	1.4 (1.2–1.8)
	Colon	1.37 (0.15)	0.42 (0.02)	< 0.0001	3.2 (2.5-4.1)	1.5 (1.1–1.8)	1.3 (1.0–1.7)
	Esophageal	0.03 (0.01)	0.03 (0.01)	0.95	1.0 (0.5–2.1)	0.4 (0.2–0.9)	0.6 (0.3–1.4)
	Liver	0.12 (0.04)	0.03 (0.01)	0.022	3.7 (1.8–7.6)	1.9 (0.9–4.0)	1.8 (0.9–3.4)
	Pancreatic	0.16 (0.07)	0.02 (0.01)	0.034	7.0 (2.8–17.3)	3.4 (1.4–8.3)	4.6 (1.8–11.7
	Rectal	0.14 (0.04)	0.03 (0.01)	0.003	4.7 (2.6–8.8)	2.1 (1.1–4.0)	2.2 (1.0-4.7)
	Stomach	0.09 (0.03)	0.04 (0.01)	0.12	2.2 (1.0-4.5)	1.1 (0.5–2.2)	1.0 (0.4–2.5)
Leukemia/lymphoma	Stofficeri	0.68 (0.10)	0.44 (0.04)	0.026	1.6 (1.1–2.2)	1.0 (0.7–1.4)	1.1 (0.8–1.6)
Leukennarymphonia	Hodgkin's	0.32 (0.08)	0.14 (0.02)	0.023	2.4 (1.4–4.1)	1.7 (0.9–3.0)	1.8 (0.9–3.4)
	lymphoma	0.92 (0.00)	0.11(0.02)	0.025	2.1 (1.1 1.1)	1.7 (0.9 9.0)	1.0 (0.9 5.1)
	Leukemia	0.15 (0.04)	0.13 (0.02)	0.61	1.2 (0.7–2.1)	0.7 (0.4–1.2)	0.8 (0.5–1.6)
	Non–Hodgkin's	0.21 (0.05)	0.17 (0.03)	0.53	1.2 (0.7–2.2)	0.8 (0.5–1.4)	0.8 (0.4–1.4)
	lymphoma	0.21 (0.05)	0.17 (0.05)	0.55	1.2 (0.7-2.2)	0.0 (0.9-1.1)	0.0 (0.1–1.1)
Skin	lymphoma	5.57 (0.27)	3.09 (0.06)	< 0.0001	1.8 (1.6–2.0)	0.9 (0.8–1.0)	1.0 (0.9–1.1)
SKIII	Melanoma	2.01 (0.15)	0.99 (0.04)	< 0.0001	2.0 (1.7–2.4)	1.0 (0.8–1.2)	1.0(0.9-1.1) 1.1(0.9-1.3)
	Other skin	3.71 (0.23)	2.14 (0.05)	<0.0001	1.7 (1.5-2.0)	0.9 (0.8–1.0)	1.0 (0.9–1.1)
Lung	Other Skill	0.38 (0.06)	0.19 (0.02)	0.0036	2.0 (1.3–2.9)	0.9 (0.6–1.3)	0.8 (0.5–1.4)
Lung Urinary		1.35 (0.14)	0.33 (0.02)	< 0.0001	4.1 (3.2–5.1)	1.8 (1.4–2.3)	1.7 (1.3-2.2)
	Bladder	0.86 (0.11)	0.22 (0.02)	< 0.0001	4.0 (3.0–5.3)	1.7(1.3-2.3)	1.7 (1.2–2.2)
	Kidney	0.50 (0.11)	0.12 (0.02)	< 0.0001	4.3 (2.9–6.4)	2.2 (1.4–3.3)	1.7(1.2-2.2) 1.9(1.2-3.0)
Other cites	Klulley		0.70 (0.04)	< 0.0001	2.2 (1.8–2.7)	1.2(1.4-3.3) 1.2(1.0-1.5)	1.9 (1.2–3.0) 1.2 (1.0–1.6)
Other sites	Uport	1.53 (0.15)			2.2 (1.0-2.7)	1.2 (1.0–1.3)	1.2 (1.0-1.0)
	Heart Bone	Rare§	Rare	0.29	$\frac{-}{10(0740)}$	-	15(0627)
	Brain	0.11 (0.04)	0.06 (0.02)	0.28	1.9(0.7-4.9)	1.6(0.7-3.9)	1.5 (0.6–3.7)
	Neuroblastoma	0.07 (0.03)	0.04 (0.01)	0.33	1.7 (0.7–3.9)	1.6 (0.7–4.0)	2.2 (0.9–5.6)
		Rare	Rare		-	-	-
137 NT	Other	1.36 (0.14)	0.60 (0.03)	< 0.0001	2.3 (1.8–2.8)	1.2 (0.9–1.5)	1.2 (1.0–1.5)
Women, N	A 11	28,699	217,625	<0.0001	17(1(17))	11(1011)	11/11 12)
D	All cancers	17.08 (0.39)	10.37 (0.11)	< 0.0001	1.7 (1.6–1.7)	1.1 (1.0–1.1)	1.1 (1.1–1.2)
Breast		5.52 (0.24)	2.87 (0.06)	< 0.0001	1.9 (1.8–2.1)	1.1(1.0-1.2)	1.1 (1.0–1.3)
Reproductive	$c \cdot 1$	4.08 (0.25)	2.22 (0.06)	< 0.0001	1.8(1.6-2.1)	1.5(1.3-1.7)	1.3 (1.2–1.6)
	Cervical	1.87 (0.15)	1.36 (0.05)	0.0011	1.4(1.2-1.6)	1.3(1.1-1.6)	1.2 (1.0–1.5)
	Endometrial	1.45 (0.17)	0.45 (0.02)	< 0.0001	3.2 (2.5-4.1)	2.0 (1.6–2.6)	1.6 (1.2–2.0)
TT 1/ 1	Ovarian	0.87 (0.13)	0.44 (0.03)	0.0011	2.0 (1.4–2.7)	1.5 (1.1–2.1)	1.4 (0.9–2.0)
Head/neck	· · · · · ·	0.67 (0.08)	0.42 (0.02)	0.0023	1.6 (1.2–2.1)	1.1 (0.8–1.4)	1.1 (0.8–1.5)
	Head and neck	0.07 (0.02)	0.05 (0.01)	0.38	1.4 (0.7–2.9)	0.8 (0.4–1.7)	1.1 (0.5–2.2)
	Oral	0.07 (0.03)	0.03 (0.01)	0.21	2.0 (0.8–4.7)	1.1 (0.4–2.6)	1.0 (0.3–3.0)
	Pharyngeal	0.06 (0.02)	0.03 (0.005)	0.18	2.2 (0.9–5.0)	1.3 (0.5–3.1)	1.3 (0.6–3.0)
	Thyroid	0.48 (0.07)	0.31 (0.02)	0.019	1.5 (1.1–2.1)	1.1 (0.8–1.5)	1.1 (0.8–1.6)
Gastrointestinal		1.42 (0.12)	0.59 (0.03)	< 0.0001	2.4 (2.0–2.9)	1.3 (1.1–1.5)	1.2 (0.9–1.5)
	Colon	1.12 (0.10)	0.47 (0.02)	< 0.0001	2.4 (2.0–2.9)	1.3 (1.0–1.6)	1.1 (0.9–1.4)
	Esophageal	Rare	0.02 (0.003)	—	—	—	—
	Liver	0.10 (0.04)	0.02 (0.01)	0.071	4.7 (1.7–12.7)	3.2 (1.1–9.3)	2.9 (0.9–9.6)
	Pancreatic	0.08 (0.03)	0.02 (0.005)	0.032	3.6 (1.6–7.8)	2.0 (0.9–4.4)	2.5 (0.9–6.8)
	Rectal	0.08 (0.03)	0.04 (0.01)	0.11	2.2 (1.1-4.7)	1.2 (0.6–2.4)	1.2 (0.5–2.8)

Table 1—Continued

Cancer site/tract	Cancer type	Crude prevalence, % (SE)			Prevalence ratio (95% CI)		
		Diabetes	No diabetes	Р	Model 1*	Model 2†	Model 3‡
	Stomach	0.04 (0.01)	0.03 (0.01)	0.40	1.4 (0.7–3.0)	0.8 (0.4–1.7)	0.9 (0.4–2.0)
Leukemia/lymphoma		0.63 (0.09)	0.36 (0.02)	0.0019	1.8 (1.3–2.4)	1.1 (0.9–1.5)	1.2 (0.8–1.6)
	Hodgkin's lymphoma	0.17 (0.05)	0.12 (0.01)	0.34	1.4 (0.8–2.5)	1.0 (0.5–1.8)	1.0 (0.5–1.8)
	Leukemia	0.30 (0.06)	0.10 (0.01)	0.0015	3.1 (1.9-4.9)	2.0 (1.3-3.4)	2.3 (1.3-4.2)
	Non–Hodgkin's lymphoma	0.16 (0.03)	0.14 (0.01)	0.51	1.2 (0.8–1.8)	0.7 (0.5–1.1)	0.7 (0.4–1.1)
Skin	7 1	4.35 (0.20)	3.25 (0.06)	< 0.0001	1.3 (1.2–1.5)	0.8 (0.7-0.9)	1.0 (0.9–1.2)
	Melanoma	1.35 (0.12)	0.90 (0.03)	0.0004	1.5 (1.2–1.8)	0.9 (0.8–1.1)	1.2 (1.0–1.5)
	Other skin	3.08 (0.16)	2.39 (0.05)	0.0001	1.3 (1.2–1.4)	0.7 (0.7–0.8)	1.0 (0.9–1.1)
Lung		0.37 (0.05)	0.24 (0.02)	0.0314	1.5 (1.1–2.2)	0.8 (0.6–1.2)	0.7 (0.4–1.1)
Urinary		0.43 (0.06)	0.19 (0.01)	0.0002	2.3 (1.7–3.2)	1.2 (0.9–1.7)	1.2 (0.8–1.6)
	Bladder	0.19 (0.04)	0.10 (0.01)	0.009	2.0 (1.3-3.0)	1.0 (0.7–1.5)	0.9 (0.6–1.3)
	Kidney	0.24 (0.05)	0.09 (0.01)	0.0071	2.6 (1.6-4.4)	1.6 (1.0-2.6)	1.6 (0.9–2.7)
Other sites		1.60 (0.15)	0.84 (0.04)	< 0.0001	1.9 (1.6–2.3)	1.3 (1.0–1.5)	1.2 (0.9–1.4)
	Heart	Rare	Rare	_	_	_	_
	Bone	0.05 (0.02)	0.05 (0.01)	0.94	1.0 (0.5–2.1)	0.9 (0.4–1.7)	0.9 (0.4–2.0)
	Brain	0.04 (0.02)	0.06 (0.01)	0.54	0.7 (0.3–2.1)	0.8 (0.3–2.1)	0.7 (0.2–2.8)
	Neuroblastoma	Rare	Rare		—	—	_
	Other	1.50 (0.14)	0.73 (0.03)	< 0.0001	2.1 (1.7–2.5)	1.3 (1.1–1.6)	1.2 (1.0–1.5)

*Model 1: unadjusted. †Model 2: adjusted for age (years, continuous) only. ‡Model 3: adjusted for age (years, continuous), race/ethnicity (non–Hispanic white, non– Hispanic black, Hispanic, other), health insurance coverage (any vs. none), smoking status (current smoker, former smoker, never smoked), heavy drinking (yes, consuming more than two drinks per day among men and more than one drink per day among women vs. no), BMI (kg/m², continuous), and physical inactivity (yes vs. no). §Rare: prevalence estimate is between 0 and 0.01%. Statistical tests are not provided due to insufficient data.

equality in the prevalence estimates was tested with a two-sample *t* test. We considered results with a two-tailed *P* value <0.05 or the 95% CI of a prevalence ratio estimate that did not include 1 to be statistically significant.

We conducted all analyses using SUDAAN 9.0 software (Research Triangle Institute, Research Triangle Park, NC) to account for the complex sampling design.

RESULTS—The final analytic sample of 397,783 individuals (mean age, 46.8 years; range, 18–99 years or older; SE = 0.06 years) consisted of 151,459 men (38.1%), 318,070 non–Hispanic whites (80.0%), 31,168 non–Hispanic blacks (7.8%), 26,764 Hispanics (6.7%), and 21,781 other racial/ethnic participants (5.5%).

After adjustment for age and all other potential confounders, men with diabetes had significantly higher prevalences of cancer of all sites and cancers of the prostate, colon, pancreas, rectum, urinary bladder, and kidney than men without diabetes (Table 1). Women with diabetes had significantly higher prevalences of cancer of all sites and cancers of the breast and endometrium as well as leukemia than women without diabetes (all P < 0.05). Diabetic men had a higher prevalence of liver cancer, whereas diabetic women had a higher prevalence of liver cancer and pancreatic cancer than their nondiabetic counterparts, albeit no statistical significance was detected (P = 0.07-0.13).

CONCLUSIONS—Our prevalence ratio estimates for the cancer of all sites among men and women were comparable to relative risk estimates in studies on cancer incidence (3,9). Our results support an association between diabetes and cancer. Previous findings have shown that diabetes is linked to an increased risk of cancers of the pancreas, liver, kidney, colorectal, urinary bladder, endometrium, breast, and non–Hodgkin's lymphoma (3). The possible biologic mechanisms that link diabetes and cancer include hyperinsulinemia, hyperglycemia, and/or chronic inflammation (2).

These findings have significant public health implications because the strong associations of diabetes with certain cancer types may inform public health decisions and policies regarding the priorities of cancer screening and clinical management. Regular screening is an important tool to detect certain types of cancer early in their onset, particularly those with high prevalence among adults with diabetes. As shown in a previous study (10), U.S. women with diagnosed diabetes had low rates of screening for cancers of the breast, cervix, colon and rectum compared with recommended levels. Moreover, diabetic women were less likely to be screened for cervical cancer compared with nondiabetic women. Therefore, enhanced efforts may be needed to promote cancer screening, particularly for the cancers highly related to diabetes, as evidenced in our study.

Our results were subject to several limitations. First, although there is a substantial agreement in determinations of diabetes status by self-reports and those based on actual diagnoses (11), misclassification bias of the diabetes status of participants with undiagnosed diabetes could have resulted in the underestimation of our results. Second, the BRFSS survey excludes adults who have been institutionalized or hospitalized and those with only mobile telephones, which may have led us to underestimate the true prevalence of cancer.

In conclusion, our results suggest that adults with diabetes had a higher prevalence of cancer than those without diabetes. These findings highlight a need for increased attention to and efforts in

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preventing and screening for certain cancers to reduce the disease burden and improve the quality of life among adults with diabetes in the general population.

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C.L. provided the study concept and design, acquired data, analyzed and interpreted data, provided statistical analysis, wrote the manuscript, and reviewed and edited the manuscript. L.S.B. and E.S.F. provided the study concept and design, interpreted data, reviewed and edited the manuscript, and supervised the study. C.A.O., J.T., and G.Z. provided the study concept and design, interpreted data, and reviewed and edited the manuscript.

References

 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

- 2. Giovannucci E, Harlan DM, Archer MC, et al. Diabetes and cancer: a consensus report. CA Cancer J Clin 2010;60:207– 221
- Vigneri P, Frasca F, Sciacca L, Pandini G, Vigneri R. Diabetes and cancer. Endocr Relat Cancer 2009;16:1103–1123
- 4. Barone BB, Yeh HC, Snyder CF, et al. Long-term all-cause mortality in cancer patients with preexisting diabetes mellitus: a systematic review and meta-analysis. JAMA 2008;300:2754–2764
- Centers for Disease Control and Prevention. Behavioral risk factor surveillance system technical information and 2009 survey data. [Internet] 2010. Atlanta, GA, U.S. Department of Health and Human Services, Centers for Disease Control and Prevention. Available from http:// www.cdc.gov/brfss/technical_infodata/ surveydata/2009.htm. Accessed 1 August 2010
- Mokdad AH, Stroup DF, Giles WH; Behavioral Risk Factor Surveillance Team. Public health surveillance for behavioral risk factors in a changing environment.

Recommendations from the Behavioral Risk Factor Surveillance Team. MMWR Recomm Rep 2003;52:1–12

- Nelson DE, Powell-Griner E, Town M, Kovar MG. A comparison of national estimates from the National Health Interview Survey and the Behavioral Risk Factor Surveillance System. Am J Public Health 2003;93:1335–1341
- 8. Barros AJ, Hirakata VN. Alternatives for logistic regression in cross-sectional studies: an empirical comparison of models that directly estimate the prevalence ratio. BMC Med Res Methodol 2003;3:21
- 9. Simon D, Balkau B. Diabetes mellitus, hyperglycaemia and cancer. Diabetes Metab 2010;36:182–191
- Zhao G, Ford ES, Ahluwalia IB, Li C, Mokdad AH. Prevalence and trends of receipt of cancer screenings among US women with diagnosed diabetes. J Gen Intern Med 2009;24:270–275
- 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