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The association between type 2 diabetes mellitus and bladder cancer risk among postmenopausal women

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Abstract

Introduction: Evidence on the association between diabetes and risk of bladder cancer has been controversial. In addition, findings on the associations between duration of diabetes, diabetes treatment and risk of bladder cancer have been inconsistent.

Methods: A total of 148,208 participants in Women's Health Initiative study were included. Information on diabetes status, diabetes duration and treatment were collected both at baseline and during follow-up. Information on potential confounders including age, race/ethnicity, education, occupation, family history of cancer, smoking status, alcohol consumption, total physical activity, body mass index, and daily dietary intake were collected at baseline. Bladder cancer cases were collected and confirmed by a centralized review of pathology reports. Cox proportional hazards models with time-varying covariates were used to examine associations of diabetes status, duration of diabetes, and diabetes treatment with bladder cancer risk.

Results: During a median follow-up of 18.5 years, 865 bladder cancer cases were identified. There were no significant associations of diabetes, duration of diabetes, or diabetes treatment with risk of bladder cancer. Participants with prevalent diabetes did not have significantly higher risk of bladder cancer compared with those without diabetes.

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Conclusion: Diabetes was not significantly associated with risk of bladder cancer among postmenopausal women.

Introduction

Bladder cancer is the sixth most common cancer in the United States (1). It is estimated that there will be 81,190 new bladder cancer cases in 2018 (2). Bladder cancer has high recurrence rates; therefore, primary prevention is important from a public health perspective (3). Although epidemiologic evidence has suggested that women have lower risk of bladder cancer than men, women with bladder cancer often have more serious prognoses (4, 5).

Causes of bladder cancer are not yet well understood. Previous studies have suggested that potential modifiable risk factors for bladder cancer include cigarette smoking, sedentary behavior, occupational exposure to chemical materials, and diabetes (6–8).

Type 2 diabetes mellitus is one of the most prevalent chronic diseases in the United States (9). It is estimated that 12.2 % of US adults aged 18 years or older have diabetes (10). Epidemiological evidence suggests that diabetes is associated with increased risks of several types of cancers, including cancers of the breast, pancreas, liver, endometrium, colon and rectum (11–14). The biological mechanisms behind these associations are still unclear, but insulin resistance and hyperinsulinemia have been implicated (15).

Diabetes may also be associated with increased risk of bladder cancer, but evidence on this relation is limited. Findings suggest that diabetes increases the opportunity for recurrent urinary tract infections, which may be related to a higher risk of bladder cancer (16, 17). In addition, two of the factors that are related to diabetes -- insulin resistance and hyperinsulinemia -- may be involved in tumor development by increasing levels of insulin-like growth factor-1 (18, 19). Nevertheless, to date, findings from previous studies on the association between diabetes and risk of bladder cancer are inconsistent (20–26). Some studies have suggested a significant elevated risk of bladder cancer among diabetes patients compared with individuals without diabetes (21, 22, 25, 27, 28). A cohort study conducted among 37,327 postmenopausal women with 277 bladder cancer incident cases observed a significant positive association between diabetes and risk of bladder cancer (27). However, other studies did not find any significant association between diabetes and risk of bladder cancer (20, 24, 26, 29, 30). These inconsistent findings may be due to small sample sizes in earlier studies and recall and selection biases in previous case-control studies (20–23).

Previous studies on the association between diabetes duration and risk of bladder cancer have also yielded inconsistent findings (21, 26, 28, 30). A case-control study observed the highest risk of bladder cancer among people with diabetes for more than 15 years compared with those who did not have diabetes (21). However, other studies did not find a significant association between diabetes duration and risk of bladder cancer, or reported that the elevated risk of bladder cancer did not follow a linear trend with the increase in diabetes duration (26, 28, 30). These divergent findings may be due to small numbers of bladder cases and different duration categories in previous studies (31). Associations of insulin, metformin, and thiazolidinedione with bladder cancer are currently unclear (21, 30, 32).

To date, only two cohort studies have examined the association between diabetes and risk of bladder cancer among postmenopausal women, both of which included few cases of bladder cancer (25, 27). Therefore, we examined associations of diabetes, diabetes duration, and diabetes treatment with risk of bladder cancer among a large prospective study of postmenopausal women. Our study was strengthened by a larger number of bladder cancer cases, recruitment sites from across the nation, and longer follow-up time compared with previous studies.

Methods

The Women's Health Initiative (WHI) Study

The WHI Study was designed to investigate major causes of morbidity and mortality among postmenopausal women. Detailed information about study rationale, inclusion criteria and recruitment methods are published elsewhere (33, 34). Briefly, a total of 161,808 postmenopausal women aged 55 to 79 were recruited into the study between 1993 and 1998 from 40 clinical centers throughout United States. The WHI includes an observational study (OS) component and three overlapping clinical trials (CTs), which consist of hormone therapy (HT), dietary modification (DM), and/or calcium and vitamin D supplementation (CaD) trials. Women from the OS and CT were included in this study. OS participants were followed up every year and those in the CTs were followed up every 6 months until 2005, at which point participants were followed up annually in the Extension Studies. We excluded women with cancer other than non-melanoma skin cancer at baseline (n = 12,600); women who enrolled but did not provide follow-up information (n = 690); whose information on diabetes status, age of diabetes diagnosis, diabetes treatments was missing (n = 185); and whose age of first diagnosis with diabetes was 21 or younger to exclude type 1 diabetes (n = 125), yielding 148,208 participants in the analytic cohort.

Exposure Measurements

Prevalence of diabetes at baseline and incidence of diabetes during follow-up before bladder cancer diagnosis were assessed. Baseline diabetes cases were identified from self-reported questionnaire by a positive answer to the question, "Did a doctor ever say that you had sugar diabetes or high blood sugar when you were not pregnant?" The incidence of treated diabetes during follow-up was determined by a positive answer to the question: "since the date given on this form has a doctor prescribed any of the following pills or treatments?" Possible answers included prescribed pills and insulin. Information on diabetes status was collected from self-reported questionnaires without ascertainment of blood glucose tests or medical records. However, it has been reported that, in WHI, self-reported diabetes information has high concordance with medical records and fasting blood glucose tests (35, 36). For example, 91.8% of the self-reported prevalent diabetes and 82.2% of incident diabetes were confirmed by medical records in a previous study, suggesting that self-reported diabetes in this study is reliable (35).

We analyzed associations between diabetes treatment and risk of bladder cancer using information from both self-reported questionnaires and medical inventory data. For self-reported diabetes, participants were categorized into no diabetes, diabetes with no treatment,

diabetes treated with pills only, or diabetes treated with insulin. Information on diabetes treatment was extracted from the WHI medicine inventory database, which was collected at baseline and year 3 for all CT and OS participants, and additionally at follow-up years 1, 6, and 9 for CT participants only. Based on the types of treatment in the medication inventory data, participants with diabetes were then categorized into five treatment groups: insulin alone or with oral medication, metformin treatment, thiazolidinediones treatment, other treatment, or treatment unknown.

The duration of prevalent diabetes was the sum of duration of diabetes at baseline (the difference between age of the participant when first diagnosed with diabetes and age at baseline) and the follow-up time. The duration of incident diabetes during follow-up was computed as the time difference between diabetes diagnosis and the end of follow-up. Diabetes duration was then categorized as less than five years and five years or more.

Potential Confounders

Confounders were chosen based on previous studies and further determined by covariates whose beta coefficients changed more than 10% after being deleted from the model, which included: age at enrollment (50–59, 60–79, 70–79), race/ethnicity (White and not of Hispanic origin, Black or African-American, or other), education (≤high school, school after high school, or ≥college degree), occupation (managerial/professional specialty, technical/ sales/administrative support, service, operator/ fabricator/ laborers, homemaker/raising children/other), family history of cancer (yes/no), recreational physical activity (0, 0.1–4.9, 5.0–9.9, 10.0–19.9, or ≥20.0 MET-hours per week), body mass index (<25.0, 25–29.9, or ≥30.0 kg/m^2), OS enrollment status (yes or no), HT trial enrollment status (not randomized in HT trial, estrogen alone intervention, estrogen alone control, estrogen plus progestin intervention, or estrogen plus progestin control). DM trial enrollment (not randomized into DM trial, intervention, or control group), and CaD trial enrollment (not randomized into CaD trial, intervention, or control). The Alternative Healthy Eating Index (AHEI)-2010 total score was used as diet quality assessment, which was computed from the food-frequency questionnaire and included the following food components: vegetables (servings/day), fruit (servings/day), whole grains (servings/day), nuts and soy protein (servings/day), long-chain fats (mg/day), polyunsaturated fat (percent of daily energy), red or processed meat (servings/ day), sodium (mg/day), trans-fat (percent of daily energy), sugar sweetened beverages and juice (servings/day), alcohol intake (g/day). All components were summed to obtain the total AHEI-2010 total score ranging from 0 as least healthy to 110 as most healthy (37, 38). Because there were more former smokers then current smokers in the WHI, smoking status and intensity were categorized as never smoker, former smokers whose years since quitting (YSQ) was <10, former smokers with 10≤YSQ<20, former smokers with 20≤YSQ<30, former smokers with YSQ≥30, current smokers smoking <15 cigarettes per day, and current smokers smoking ≥15 cigarettes per day.

Outcome

Incidence of bladder cancer was first collected through self-administered questionnaire, then reviewed and confirmed by trained central adjudicators using medical records and available pathology reports.

Statistical analysis

Participants were followed from the date of study enrolment to date of diagnosis of bladder cancer, death, loss to follow-up, or the end of the study period (i.e., March 31, 2018), whichever occurred first. Baseline characteristics were examined by diabetes status. Analysis of variance (ANOVA) tests were performed to test differences for continuous variables, chi-square tests were used to test for non-ordinal categorical variables, and Wilcoxon Rank-Sum tests were used for ordinal variables (including age, total physical activity, smoking intensity among former and current smokers, and BMI) among different diabetes groups.

Cox proportional hazards regression models with time-dependent covariates were used to evaluate associations of diabetes, diabetes treatment, and diabetes duration with risk of bladder cancer. Tests for linear-trend of diabetes duration with bladder cancer risk were performed by treating the categorical variable of diabetes duration (no diabetes, ≤5 and >5 years) as an ordinal variable in the multivariable model. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated. Models were initially adjusted for age only, then further adjusted for all confounders.

The information about urinary tract infections (UTIs) were available in WHI extension study. All participants in the WHI Extension Study received a one-time supplemental questionnaire in the third year of the extension and were asked if they were told that they had a urinary tract infection by a health care provider as well as the time since their last urinary tract infection. A sensitivity analysis was performed to consider UTIs by using WHI extension data with UTI variables included in the multivariable model.

Smoking is an established risk factor for bladder cancer (3, 6). We thus performed a sensitivity analysis stratifying data by smoking status. To account for the different follow-up duration in CT and OS studies, another sensitivity analysis was performed by only including participants in the OS study. In addition, since participants in DM trial were assigned low-fat and high-fiber diet (39), we conducted a sensitivity analysis by excluding participants from DM trial to reduce the possible impact of dietary intervention.

All statistical analyses were conducted using SAS (Version 9.4, SAS Institute, Cary, NC). Two-sided P values were reported and a $P \leq 0.05$ was considered statistically significant.

Results

There were 26,294 women with diabetes in our data, of whom 8,381 had prevalent diabetes at baseline. As of March 31, 2018, during a median 18.5 years of follow-up, 865 bladder cancer cases were diagnosed, including 766 among women without diabetes and 99 among women with diabetes.

Characteristics of participants by baseline diabetes status are shown in Table 1. Compared with women who did not have diabetes at baseline, women with diabetes were older, more likely to be non-white, have lower academic degrees, more likely to be sedentary and obese,

have lower total AHEI-2010 total score, and less likely to smoke or have family history of cancer.

In the multivariable model, compared with women without diabetes, women with diabetes did not have significantly increased risk of bladder cancer (HR=1.03, 95% CI: 0.83–1.29), even after adjusting for treatment status or types of medications (Table 2).

Findings were similar when using medication inventory instead of self-reported data for diabetes treatment. There was no association between diabetes duration and bladder cancer (Table 2). When additionally adjusted for urinary tract infection status in the sensitivity analysis, the results followed similar pattern as from the primary analysis (Table S1). Stratified analysis due to smoking also yield to similar results with the primary analysis (Table S2). When including only participants in OS study, the results followed same pattern with the primary analysis (Table S3). Similarly, when excluding participants from DM trial, the results did not appreciably alter (Data not shown).

Discussion

In this large, prospective study of postmenopausal women followed for up to 25 years, we observed no associations of diabetes, diabetes duration, or diabetes treatment with risk of bladder cancer among postmenopausal women.

Previous findings on the risk of bladder cancer among diabetic populations in comparison to people without diabetes have been inconsistent (20–23, 29, 30). We found an increased but non-significant association between diabetes and risk of bladder cancer, which is consistent with some previous studies (20, 23, 29, 30, 40). However, in other studies, diabetes was associated with bladder cancer (29, 41). A cohort study including 37,327 women from the Iowa Women's Health Study reported a significantly increased risk of bladder cancer among postmenopausal white women with baseline diabetes (25, 27). The reasons giving rise to the difference in results is unclear. One reason could be that the association between diabetes and risk of bladder cancer is too weak to detect, even with a large sample size and long follow-up time. We did not detect a significant relationship between insulin use and risk of bladder cancer, which is in agreement with most studies (21, 24, 42).

Findings from the few studies examining duration of diabetes and risk of bladder cancer have been inconsistent (21, 26, 28, 30). We did not observe associations of diabetes duration with bladder cancer risk, which is consistent with findings from some previous studies (26, 30). A case-control study found that people with 5 or more years of diabetes had higher odds of bladder cancer, and the risk of bladder cancer increased with duration of diabetes (21). A cohort study with 216 bladder cancer cases found that the duration of diabetes was not associated with bladder cancer, with a risk ratio (RR) of 1.13 (95% CI: 0.84–1.53) for those who had diabetes for ≥15 years (30). Another cohort study found that in comparison to people without diabetes, the risk of bladder cancer was highest among people who had diabetes for 1–3 years, and the risk dropped slightly for those who had diabetes for more than five (28). In sum, the association between duration of diabetes and risk of bladder cancer remains unclear and needs further investigation.

Our observed null association between diabetes and risk of bladder cancer may be a result of several factors. First, the association between diabetes and bladder cancer risk may be null or weak. Information on diabetes was based on self-reported questionnaire and diabetes medication use, and may have misclassification, especially for the incident diabetes. However, two previous validation studies in the WHI have reported that self-reported diabetes is reliable compared with review of medical records (35, 36). Age of diabetes diagnosis for the participants with prevalent diabetes was also accessed from self-administrated questionnaires, which subject to recall bias. In addition, information on confounders was collected at baseline, some of which may have changed since baseline, yet we did not examine time-varying confounders. There may be systematic errors for self-reported diet; for example, people with higher BMI tend to underreport their daily energy intake (39). Furthermore, despite the fact that WHI is one of the largest prospective studies in the United States, the number of bladder cancer cases may still not have been large enough to detect any association between diabetes, diabetes duration, or different types of diabetes treatment and risk of bladder cancer.

Important strengths of this study include the prospective study design with long follow-up period among a large, ethnically diverse cohort. Information on a large number of covariates was available, and bladder cancer cases were ascertained by central adjudication.

Conclusion

Findings from this study do not support associations of diabetes, diabetes duration, or diabetes treatment with risk of bladder cancer among postmenopausal women. Further studies with objective measurements of diabetes and blood glucose control assessments are needed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix

SHORT LIST OF WHI INVESTIGATORS

Program Office:

(National Heart, Lung, and Blood Institute, Bethesda, Maryland) Jacques Rossouw, Shari Ludlam, Joan McGowan, Leslie Ford, and Nancy Geller

Clinical Coordinating Center:

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(Brigham and Women's Hospital, Harvard Medical School, Boston, MA) JoAnn E. Manson; (MedStar Health Research Institute/Howard University, Washington, DC) Barbara V. Howard; (Stanford Prevention Research Center, Stanford, CA) Marcia L. Stefanick; (The Ohio State University, Columbus, OH) Rebecca Jackson; (University of Arizona, Tucson/Phoenix, AZ) Cynthia A. Thomson; (University at Buffalo, Buffalo, NY) Jean Wactawski-Wende; (University of Florida, Gainesville/Jacksonville, FL) Marian Limacher; (University of Iowa, Iowa City/Davenport, IA) Jennifer Robinson; (University of Pittsburgh, Pittsburgh, PA) Lewis Kuller; (Wake Forest University School of Medicine, Winston-Salem, NC) Sally Shumaker; (University of Nevada, Reno, NV) Robert Brunner; (University of Minnesota, Minneapolis, MN) Karen L. Margolis

Women's Health Initiative Memory Study:

(Wake Forest University School of Medicine, Winston-Salem, NC) Mark Espeland

For a list of all the investigators who have contributed to WHI science, please visit: https://www.whi.org/researchers/Documents%20%20Write%20a%20Paper/WHI%20Investigator%20Long%20List.pd

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Table 1.

Baseline characteristics of participants by diabetes status at baseline.

	Diabetes		
Variable*	**Yes (n=8381)**	**No (n=139,827)**	**P-value****
Age at screening (%)			<.0001
50–59	2152(25.7)	47,563(34.0)	
60–69	4,131(49.3)	62,497(44.7)	
70–79	2,098(25.0)	29,767(21.3)	
Race/ethnicity (%)			<.0001
White (not of Hispanic origin)	5,491(65.7)	116,871(83.8)	
Black/African-American	1,800(21.5)	11,522(8.3)	
Other	1,065(12.8)	11,101(8.0)	
Education (%)			<.0001
≤ High school	2,660(32.0)	30,473(22.0)	
School after high school	3,379(40.6)	52,315(37.7)	
College degree or higher	2,279(27.4)	56,002(40.4)	
Occupation (%)			<.0001
Managerial/professional	2,653(34.6)	54,459(42.5)	
Tech/sales/administrative	2,160(28.2)	38,176(29.8)	
Service/labor	1,891(24.7)	22,272(17.4)	
Homemaker only/other	954(12.5)	13,252(10.3)	
Smoking status (%)			<.0001
Never smokers	4,277(52.0)	70,702(51.2)	
Former smokers	3,388(41.2)	57,782(41.9)	
Current smokers	562(6.8)	9,569(6.9)	
Smoking intensity			
Never smokers	4,277(53.4)	70,702(52.6)	<.0001
Former smokers			<.0001
YSQ<10	750(9.4)	14,473(10.8)	
10≤YSQ<20	738(9.2)	14,011(10.4)	
20≤YSQ<30	935(11.7)	14,535(10.8)	
YSQ≥30	748(9.3)	11,103(8.3)	
Current smokers			<.0001
Cigarettes/day<15	292(3.7)	4,992(3.7)	
Cigarettes/day≥15	270(3.4)	4,577(3.4)	
BMI (%, kg/m^2)			<.0001
Underweight or Normal (<25.0)	1183(14.1)	51,726(37.0)	
Overweight (25.0 – 29.9)	2,359(28.2)	48,805(34.9)	
Obesity (≥30.0)	4,839(57.7)	39,296(28.1)	

	Diabetes		
Variable*	**Yes (n=8381)**	**No (n=139,827)**	**P-value****
Physical activity (MET-hours/week) (%)			<.0001
0	1,754(21.83)	20,500(15.44)	
0.1–4.9	2,150(26.75)	27,445(20.7)	
5.0–9.9	1,438(17.9)	22,951(17.3)	
10.0–19.9	1,560(19.4)	32,277(24.3)	
≥ 20	1,134(14.1)	29,606(22.3)	
Family history of cancer (%)	5,081(62.7)	88,631(65.4)	<.0001
Observational Study (%)	4,378(52.2)	78,453(56.1)	<.0001
HT trial (%)			<.0001
Not randomized to HT	6,521(77.8)	115,285(82.5)	
E-alone intervention	465(5.6)	4,588(3.3)	
E-alone control	476(5.7)	4,642(3.3)	
E+P intervention	467(5.6)	7,846(5.6)	
E+P control	452(5.4)	7,466(5.3)	
DM trial (%)			0.07
Not randomized to DM	5,642(67.3)	95,798(68.5)	
Intervention	1,093(13.0)	17,634(12.6)	
Control	1,646(19.6)	26,395(18.9)	
CaD trial (%)			0.77
Not randomized to CaD	6,429(76.7)	106,828(76.4)	
Intervention	983(11.7)	16,501(11.8)	
Control	969(11.6)	16,498(11.8)	
Total AHEI-2010 diet score	51.3(10.1)	52.0(10.4)	<.0001

Abbreviation: HT, Hormone Therapy; E, estrogen; P, progestin; DM, Dietary Modification; CaD, Calcium and Vitamin D; BMI, body mass index; SD, standard deviation; YSQ, years since quitting. AHEI, Alternative Healthy Eating index.

*Values are (n, %), if not specified.

**P-values were computed for comparison of differences between women with and without diabetes at baseline. The differences for continuous variables were tested by Analysis of Variance (ANOVA) tests, non-ordinal categorical variables for tested by chi-square tests, and ordinal variables (including age, total physical activity, smoking intensity among former and current smokers, and BMI) were tested by the Wilcoxon Rank-Sum tests.

Table 2.

Hazard ratios (HRs) and 95% confidence intervals (95% CIs) for the association between diabetes, diabetes duration, diabetes treatment and risk of bladder cancer [*].

	No. of bladder cancer cases	Person-years	Incidence rate (per 10000)	Age-adjusted HR (95%CI)	Multivariable-adjusted HR (95% CI) [**]
Diabetes status					
No diabetes	766	2,062,095	3.71	1.00	1.00
Treated diabetes	99	231,499	4.28	1.01 (0.82–1.24)	1.03 (0.83–1.29)
Diabetes treatment from self-reported					
No diabetes or no treatment	766	2,062,095	3.71	1.00	1.00
Diabetes treated with pills only	74	167,545	4.42	1.04 (0.81–1.34)	1.08 (0.83–1.39)
Diabetes treated with insulin	25	63,954	3.91	0.89 (0.62–1.28)	0.91 (0.63–1.32)
Diabetes treatment from medication inventory					
No diabetes	766	2,062,095	3.71	1.00	1.00
Insulin (alone or with oral medication)	13	31,259	4.16	0.89 (0.41–1.67)	0.76 (0.27–1.65)
Metformin	19	54,013	3.52	0.88 (0.40–1.65)	0.84 (0.33–1.72)
Thiazolidinediones	12	18,603	6.45	1.30 (0.62–2.36)	1.27 (0.54–2.48)
Other medication	9	25,043	3.59	0.95 (0.47–1.69)	0.92 (0.44–1.73)
Treatment unknown or untreated diabetes	46	97,602	4.71	0.55 (0.44–0.68)	0.37 (0.22–0.58)
Diabetes duration					
No diabetes	766	2,062,095	3.71	1.00	1.00
≤5 years	40	104,018	1.84	0.94 (0.69–1.30)	0.93 (0.68–1.29)
>5 years	59	127,482	4.63	1.06 (0.81–1.38)	1.09 (0.83–1.46)
P-for linear trend				0.38	0.19
Linear association (per 1-year increments)				1.01 (0.90–1.31)	1.14 (0.96–1.37)

[*] Time-varying Cox models were applied to assess the associations

[**] Multi-variable adjusted model was adjusted for age, race/ethnicity, education, occupation, family history of cancer, study cohorts, smoking status and intensity, total physical activity, BMI, AHEI-2010 total score.