Published in final edited form as:
Cancer Epidemiol. 2011 December ; 35(6): 551–554. doi:10.1016/j.canep.2011.02.014.

Diabetes and urothelial cancer risk: The Multiethnic Cohort Study

Christy G. Woolcott[a], **Gertraud Maskarinec**[b], **Christopher A. Haiman**[c], **Brian E. Henderson**[c], and **Laurence N. Kolonel**[b,*]

[a]Perinatal Epidemiology Research Unit, Departments of Obstetrics & Gynecology and Pediatrics, Dalhousie University, Halifax, NS, Canada

[b]Cancer Research Center of Hawaii, University of Hawaii, Honolulu, HI, USA

[c]Department of Preventive Medicine, Norris Comprehensive Cancer Center, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA

Abstract

Background—It is important to understand the adverse health sequelae that may result from the rising incidence of diabetes. Diabetics may have an increased risk for urothelial cancer but the evidence from prospective studies and ethnically diverse populations is sparse.

Method—We examined this association in the Multiethnic Cohort (MEC) that was conducted in Hawaii and Los Angeles with nearly 186,000 participants in five ethnic groups. Over a median 10.7 years of follow-up, 918 incident cases of urothelial cancer (89% bladder and 11% other urinary tract sites) were identified through tumor registry linkages.

Results—A self-reported diagnosis of diabetes was associated with an increased risk of urothelial cancer (relative risk = 1.25; 95% confidence interval: 1.04–1.50). The association was not explained by body mass index, physical activity, or smoking. There was some suggestion that the risk was higher in women, Whites and African Americans, and past smokers. The risk associated with diabetes for *in situ* and localized cancer was similar to that for regional and distant cancer.

Conclusion—This study demonstrates that the increased urothelial cancer risk with diabetes in this multiethnic population is very similar to that observed in mostly White or Asian populations. Whether or not the elevated risk is moderated by the degree of control of the hyperglycemia associated with diabetes will need to be determined in future studies.

Keywords

Diabetes; Urothelial cancer; Bladder cancer; Prospective cohort; Epidemiology

[*]*Corresponding author:* Address: Cancer Research Center of Hawaii, University of Hawaii, 1236 Lauhala Street, Honolulu, HI 96813, USA. Tel.: 808 586 2986; fax: 808 586 2982. lkolonel@crch.hawaii.edu (LN Kolonel).

Conflict of interest statement None declared.

1. Introduction

Bladder cancer is the fifth most common cancer in the United States [1]. Known risk factors include age, sex (male), ethnicity/race (White), smoking, and several occupations, particularly those involving exposure to aromatic amines [2]. Evidence is accumulating that diabetes may be related to the risk of several cancers including a reduced risk for prostate cancer[3] and increased risks for cancers of the pancreas, liver, colon, and breast [4,5], but the evidence is not as clear for bladder cancer. A meta-analysis published in 2006 estimated that diabetics had a slightly elevated risk of bladder cancer relative to nondiabetics [6]. Significant heterogeneity by study design was observed; over the seven case-control and the three prospective cohort studies, increased risks were observed but not in the six retrospective cohorts of diabetic patients. Furthermore, a significant association was not observed in a prospective cohort study published after this meta-analysis [7]. Of the four prospective cohort studies reported to date, three were based on largely White populations [4,7,8] and the other was completed among a Korean population [5]. It is important to understand the adverse health sequelae that may result from the rising incidence of diabetes but the evidence regarding its impact on bladder cancer risk from prospective studies and ethnically diverse populations is sparse and unclear. Because the incidence of both diabetes [9,10] and bladder cancer [2] varies by ethnic group, we thought it important to examine their association in the Multiethnic Cohort (MEC) with representation from five main ethnic groups: Japanese American, White, Latino, African American, and Native Hawaiian.

2. Materials and Methods

2.1. The Multiethnic Cohort Study

Details about the MEC have been published previously.[11] The study was approved by the institutional review boards at the University of Hawaii and the University of Southern California. Over 215,000 people from Hawaii and Los Angeles aged 45 to 75 completed a self-administered questionnaire and returned it by mail between 1993 and 1996. Information was collected about demographic factors, weight and height, smoking, diet, physical activity, work history, and medical conditions. Physical activity was represented by the sum of the time spent doing moderate activities, vigorous work, and strenuous sports in an average week over the past year. Participants were defined as having diabetes at baseline if in response to the question, “Has your doctor ever told you that you had any of the following?” they checked “diabetes (high blood sugar).” People reporting mixed ancestry were assigned to a single group based on the priority ranking: African American, Native Hawaiian, Latino, Japanese American, and White. Excluded were 13,991 people who did not belong to one of the five targeted ethnic groups, 6,654 people with prevalent self-reported or cancer registry-detected diagnoses of urothelial cancers at baseline, 8,264 people who had implausible dietary responses, and 7,135 people with missing smoking information.

2.2. Identification of urothelial cancer cases

For this analysis, follow-up was accrued until a diagnosis of urothelial cancer, death, or 31 December 2004. Incident cancer diagnoses, with information about histology and stage, were identified by linkage with population-based cancer Surveillance, Epidemiology and End Results (SEER) Program registries: the Hawaii Tumor Registry, the Los Angeles County Cancer Surveillance Program, and the State of California Cancer Registry. Deaths were identified by linkage with the databases of the Hawaii and California vital statistics offices and the National Death Index. Included as cancer cases were 918 people diagnosed with transitional cell carcinomas (ICDO2 histology codes 8050, 8120, 8121, 8122, 8123, 8124, 8130, or 8131) of the urinary tract, including the bladder (ICDO2 site 67.0–67.9; *N* =

818), renal pelvis (ICDO2 site 65.9; *N* = 57), ureter (ICDO2 site 66.9; *N* = 34), and other urinary organs (ICDO2 site 68.9; *N* = 9).

2.3. Statistical analysis

The association between diabetes status and urothelial cancer risk was assessed by estimating relative risks (RR) in Cox proportional hazards models using age as the time metric. Note that in survival analysis, the association of interest is assumed to be the same in participants censored due to death or the end of followup as in participants not censored. Adjustment was made for known bladder cancer risk factors: the models used ethnicity and sex as strata variables and included smoking status (never, past, current), smoking intensity (continuous), smoking duration (continuous), and employment in a high risk industry (no, yes). Smoking duration was treated as a time-dependent covariate such that the duration of smoking for smokers at baseline was reduced by a proportion according to the estimated cessation rates. Smoking cessation rates by sex and ethnic group were estimated from 5,090 participants for whom information was available at the time of this analysis from a comprehensive follow-up questionnaire that was completed starting in 2003 [12]. Other covariates, including education, family history of urothelial cancer in a first degree relative, coffee intake, and alcohol intake, did not affect the estimates of the association between diabetes and urothelial cancer risk by more than 5%, and thus were not deemed to be confounders in this population. Finally, adjustment was made for body mass index (BMI) and physical activity and the percent change in the parameter estimates associated with diabetes was calculated. Subgroup analyses were done by sex, ethnicity, smoking status, and stage. Subgroups with fewer than 20 diabetic cases were excluded. The two stage subgroups were: 1) SEER stage 0 (*in situ*) and 1 (localized), and 2) SEER stage 2, 3, 4, 5 (regional), and 7 (distant). Analyses were done using SAS 9.2 (SAS Institute Inc., Cary, NC).

3. Results

Included in this study were 185,816 MEC participants with a median follow-up time of 10.7 years, during which 918 cases of urothelial cancer were diagnosed. At baseline, the mean (SD) age of the cohort participants was 60.4 (8.9) years (Table 1). Of the participants, 29% were Japanese American, 25% were White, 22% were Latino, 17% were African American and 7% were Native Hawaiian. Relative to participants without diabetes, diabetics were less likely to be White and more likely to be African American, Native Hawaiian, or Latino. Diabetics also had higher BMI and smoking, and lower physical activity, coffee intake and alcohol intake.

In multivariable-adjusted analyses, participants who reported diabetes had a 25% (95% CI: 4–50%) higher risk of urothelial cancer relative to participants who did not report diabetes (Table 2). The risk for bladder cancer only (89% of the urothelial cancers) was slightly higher (RR = 1.30, 95% CI: 1.07–1.57). The number of cases of regional and distant urothelial cancers among diabetics was low, but the risk associated with diabetes was very similar to that for *in situ* and localized urothelial cancers (RR = 1.25 *versus* 1.23, respectively). Although no significant effect modification by sex, ethnicity, or smoking status was observed (*p* for heterogeneity = 0.19, 0.47, 0.64, respectively), there was some indication that the risk was higher in some subgroups (women, Whites and African Americans, past smokers). Adjustment for smoking, BMI and physical activity, known risk factors for diabetes had little effect on the estimated risks. Exclusion of smoking from the multivariable-adjusted models shown in Table 2 increased the estimated RR for the association between diabetes and urothelial cancer by 10%. Inclusion of BMI or physical activity changed the RR by 2–3%. Note that BMI and physical activity were not associated with urothelial cancer risk (*p* = 0.73 and 0.19, respectively).

4. Discussion

In this analysis of nearly 186,000 persons representing five ethnic groups, with 918 cases of urothelial cancer diagnosed over a median 10.7 years of follow-up, a self-reported diagnosis of diabetes was associated with a statistically significant 25% increased risk of urothelial cancer. This result is very close to that observed in a meta-analysis (RR = 1.24, 95% CI: 1.08–1.42; ref. [6]) and not inconsistent with that observed in a more recent prospective cohort (RR = 1.16, 95% CI: 0.81–1.64; ref. [7]). In the current study, there was some suggestion that the risk associated with diabetes was higher in Whites and African Americans, past smokers, and women. Likewise, the risk estimated from a cohort of women [8] was higher than in a cohort of men [7], and the association between blood glucose levels and bladder cancer was stronger in women than in men in a very large cohort [13]. Other studies that examined the association with bladder cancer mortality, however, found it to be either slightly stronger in men than women [4], or similar in men and women [14]. We did not find evidence for an association within Japanese Americans, in contrast to other studies among Asian populations, including Korean men [5] and Taiwanese men and women [14]. Ours is the first study to suggest that the association may also be apparent among African Americans.

The association between diabetes and bladder cancer persists after adjustment for several factors. Although BMI and physical activity are strong risk factors for diabetes [15], they are not strongly associated with bladder cancer risk [7,16,17]. Smoking, an important risk factor for bladder cancer [2], is also moderately associated with diabetes risk [18] but this concordance is not sufficient to explain the association between diabetes and bladder cancer risk. Other factors inconsistently associated with an increased risk of bladder cancer, such as the consumption of coffee and alcohol [2], are protective against the risk of diabetes [15]. Therefore, the association between diabetes and urothelial cancer is not likely to be due to these shared risk factors although other factors not considered here may explain the association.

The elevation of insulin and insulin-like growth factor-1 and their role as mitogens is the mechanism cited most often to explain the association between diabetes and cancer risk. A single case-control study has found higher circulating levels of these factors in bladder cancer cases than in controls [19]. Diabetes is also associated with changes in urine composition and bladder function that could increase the concentration of or duration of exposure to carcinogens in the urine. Increased urinary tract infections and bladder dysfunction [20] may increase bladder cancer risk via inflammation and reduced urination frequency [21,22]. The reduced urinary pH occurring in diabetes [23] may render aromatic amines in the urine actively carcinogenic [24]. In one study, net acid excretion estimated from diet and BMI was related to a nonsignificantly elevated risk of bladder cancer in long-term smokers [25]; smoking is a main source of aromatic amines. In the current study, however, the association between diabetes and bladder cancer was nonsignificantly higher in past smokers than in current or never smokers. Lower urine pH is also conducive to the formation of urinary tract stones, causing urothelial inflammation and possibly leading to bladder cancer [22].

A limitation of the current study is the assessment of diabetes. The risk we have estimated based on self-reported diabetes may be an attenuation of the true risk. Of people who do not report a diabetes diagnosis, 2–8% have it based on fasting glucose or glucose tolerance tests and 74–80% of people who report a diagnosis of diabetes have it based on medication inventories or fasting glucose levels [10,26,27]. Our cohort members reported diabetes before more inclusive diagnostic criteria were introduced in 1997 [28]. If we assume a slightly lower risk of bladder cancer among diabetics with lower fasting glucose levels than

among diabetics with higher fasting glucose levels [5,13], the RR in our analysis would have been slightly lower if we had included these additional cases. Details about the diagnosis were not available to examine if the observed association was different for Type 1 *versus* Type 2 diabetes or was moderated by duration of diabetes or effective treatment. A difference in the detection of urothelial cancer by diabetes status is unlikely to explain our findings: Our results are similar for different stages of urothelial cancer, and retrospective cohorts of diabetics who were identified by virtue of their contact with the medical system have not observed an association (reviewed in ref. [6]). We were able to control for the confounding effect of several factors known to influence the risk of diabetes or bladder cancer in the general population, but unmeasured confounders have the potential to bias the observed association. Finally, our sample size was not sufficient to have much power to detect associations in subgroups.

In conclusion, an elevation in urothelial cancer risk may be associated with diabetes. Future work could be done to help to determine if detection bias or confounding explain the observed association, which biological mechanisms are most plausible, and whether or not this risk is moderated by the degree of control of the hyperglycemia associated with diabetes.

Acknowledgments

The Multiethnic Cohort Study is supported by US Public Health Service (National Cancer Institute) grant R37 CA 54281. CGW was supported by a postdoctoral fellowship on grant R25 CA 90956. The study sponsors had no role in the design and conduct of the study; data collection, analysis and interpretation; or in the preparation, review or approval of the manuscript.

Grant support: The Multiethnic Cohort Study is supported by US Public Health Service (National Cancer Institute) grant R37 CA 54281. CGW was supported by a postdoctoral fellowship on grant R25 CA 90956. The study sponsors had no role in the design and conduct of the study; data collection, analysis and interpretation; or in the preparation, review or approval of the manuscript.

References

1. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics, 2009. CA Cancer J Clin. 2009; 59:225–49. [PubMed: 19474385]
2. Silverman, DT.; Devesa, SS.; Moore, LE.; Rothman, N. Bladder cancer. In: Schottenfeld, D.; Fraumeni, JF., Jr., editors. Cancer Epidemiology and Prevention. Oxford University Press; New York: 2006. p. 1101-1150.
3. Waters KM, Henderson BE, Stram DO, Wan P, Kolonel LN, Haiman CA. Association of diabetes with prostate cancer risk in the multiethnic cohort. Am J Epidemiol. 2009; 169:937–45. [PubMed: 19240222]
4. Coughlin SS, Calle EE, Teras LR, Petrelli J, Thun MJ. Diabetes mellitus as a predictor of cancer mortality in a large cohort of US adults. Am J Epidemiol. 2004; 159:1160–7. [PubMed: 15191933]
5. Jee SH, Ohrr H, Sull JW, Yun JE, Ji M, Samet JM. Fasting serum glucose level and cancer risk in Korean men and women. JAMA. 2005; 293:194–202. [PubMed: 15644546]
6. Larsson SC, Orsini N, Brismar K, Wolk A. Diabetes mellitus and risk of bladder cancer: a meta-analysis (review). Diabetologia. 2006; 49:2819–23. [PubMed: 17021919]
7. Larsson SC, Andersson SO, Johansson JE, Wolk A. Diabetes mellitus, body size and bladder cancer risk in a prospective study of Swedish men. Eur J Cancer. 2008; 44:2655–60. [PubMed: 18707871]
8. Tripathi A, Folsom AR, Anderson KE. Risk factors for urinary bladder carcinoma in postmenopausal women. The Iowa Women's Health Study. Cancer. 2002; 95:2316–23. [PubMed: 12436437]
9. Maskarinec G, Erber E, Grandinetti A, Verheus M, Oum R, Hopping BN, et al. Diabetes incidence based on linkages with health plans: the multiethnic cohort. Diabetes. 2009; 58:1732–8. [PubMed: 19258435]

10. Grandinetti A, Kaholokula JK, Theriault AG, Mor JM, Chang HK, Waslien C. Prevalence of diabetes and glucose intolerance in an ethnically diverse rural community of Hawaii. Ethn Dis. 2007; 17:250–5. [PubMed: 17682354]
11. Kolonel LN, Henderson BE, Hankin JH, Nomura AM, Wilkens LR, Pike MC, et al. A multiethnic cohort in Hawaii and Los Angeles: baseline characteristics. Am J Epidemiol. 2000; 151:346–57. [PubMed: 10695593]
12. Haiman CA, Stram DO, Wilkens LR, Pike MC, Kolonel LN, Henderson BE, et al. Ethnic and racial differences in the smoking-related risk of lung cancer. N Engl J Med. 2006; 354:333–42. [PubMed: 16436765]
13. Stocks T, Rapp K, Bjorge T, Manjer J, Ulmer H, Selmer R, et al. Blood glucose and risk of incident and fatal cancer in the metabolic syndrome and cancer project (Me-Can): analysis of six prospective cohorts. PLoS Med. 2009; 6:e1000201. [PubMed: 20027213]
14. Tseng C-H, Chong C-K, Tseng C-P, Chan TT. Age-related risk of mortality from bladder cancer in diabetic patients: a 12-year follow-up of a national cohort in Taiwan. Ann Med. 2009; 41:371–9. [PubMed: 19191082]
15. Schulze MB, Hoffmann K, Boeing H, Linseisen J, Rohrmann S, Mohlig M, et al. An accurate risk score based on anthropometric, dietary, and lifestyle factors to predict the development of type 2 diabetes. Diabetes Care. 2007; 30:510–5. [PubMed: 17327313]
16. Koebnick C, Michaud D, Moore SC, Park Y, Hollenbeck A, Ballard-Barbash R, et al. Body mass index, physical activity, and bladder cancer in a large prospective study. Cancer Epidemiol Biomarkers Prev. 2008; 17:1214–21. [PubMed: 18483344]
17. Holick CN, Giovannucci EL, Stampfer MJ, Michaud DS. Prospective study of body mass index, height, physical activity and incidence of bladder cancer in US men and women. Int J Cancer. 2007; 120:140–6. [PubMed: 17036323]
18. Willi C, Bodenmann P, Ghali WA, Faris PD, Cornuz J. Active smoking and the risk of type 2 diabetes: a systematic review and meta-analysis. JAMA. 2007; 298:2654–64. [PubMed: 18073361]
19. Zhao H, Grossman HB, Spitz MR, Lerner SP, Zhang K, Wu X. Plasma levels of insulin-like growth factor-1 and binding protein-3, and their association with bladder cancer risk. J Urol. 2003; 169:714–7. [PubMed: 12544349]
20. Brown JS, Wessells H, Chancellor MB, Howards SS, Stamm WE, Stapleton AE, et al. Urologic complications of diabetes. Diabetes Care. 2005; 28:177–85. [PubMed: 15616253]
21. Jiang X, Castelao JE, Groshen S, Cortessis VK, Shibata DK, Conti DV, et al. Water intake and bladder cancer risk in Los Angeles County. Int J Cancer. 2008; 123:1649–56. [PubMed: 18623082]
22. Michaud DS. Chronic inflammation and bladder cancer. Urol Oncol. 2007; 25:260–8. [PubMed: 17483025]
23. Cameron MA, Maalouf NM, ms-Huet B, Moe OW, Sakhaee K. Urine composition in type 2 diabetes: predisposition to uric acid nephrolithiasis. J Am Soc Nephrol. 2006; 17:1422–8. [PubMed: 16597681]
24. Alguacil J, Pfeiffer RM, Moore LE, Del Fresno MR, Medina-Lopez R, Kogevinas M, et al. Measurement of urine pH for epidemiological studies on bladder cancer. Eur J Epidemiol. 2007; 22:91–8. [PubMed: 17334820]
25. Wright ME, Michaud DS, Pietinen P, Taylor PR, Virtamo J, Albanes D. Estimated urine pH and bladder cancer risk in a cohort of male smokers (Finland). Cancer Causes Control. 2005; 16:1117–23. [PubMed: 16184478]
26. Margolis KL, Lihong Q, Brzyski R, Bonds DE, Howard BV, Kempainen S, et al. Validity of diabetes self-reports in the Women's Health Initiative: comparison with medication inventories and fasting glucose measurements. Clin Trials. 2008; 5:240–7. [PubMed: 18559413]
27. Molenaar EA, Van Ameijden EJ, Grobbee DE, Numans ME. Comparison of routine care self-reported and biometrical data on hypertension and diabetes: results of the Utrecht Health Project. Eur J Public Health. 2007; 17:199–205. [PubMed: 16887835]

28. Expert Committee of the Diagnosis and Classification of Diabetes Mellitus. Report of the expert committee on the diagnosis and classification of diabetes mellitus. Diabetes Care. 1997; 20:1183–97. [PubMed: 9203460]

Table 1

Characteristics of the Multiethnic Cohort Study participants at baseline by diabetes status.

Characteristic	Diabetes		No diabetes	
	N	(%)	N	(%)
Total	21838	(100.0)	163978	(100.0)
Ethnicity/race				
Japanese American	5638	(25.8)	47919	(29.2)
White	2734	(12.5)	43564	(26.6)
Latino	6428	(29.4)	34442	(21.0)
African American	5022	(23.0)	26568	(16.2)
Native Hawaiian	2016	(9.2)	11485	(7.0)
Education ≤ 12th grade	12072	(55.6)	68914	(42.2)
Male	10501	(48.1)	73140	(44.6)
Ever smoker	12782	(58.5)	89354	(54.5)
Current smoker	3056	(14.0)	26772	(16.3)
High risk industry[a]	375	(1.7)	2082	(1.3)
Family history of urothelial cancer	117	(0.5)	1082	(0.7)
	Mean	**(SD)**	**Mean**	**(SD)**
Age at cohort entry (years)	62.9	(8.1)	60.1	(8.9)
Body mass index (kg/m^2)	28.7	(5.5)	26.2	(4.7)
Physical activity (hours/week)	6.8	(8.9)	8.6	(9.7)
Amount smoked (cigarettes/day)	8.7	(9.8)	8.0	(9.5)
Duration smoked (years)	13.6	(15.0)	12.2	(14.5)
Coffee intake (cups/day)	0.95	(1.13)	1.10	(1.19)
Alcohol intake (servings/day)	0.36	(1.46)	0.69	(1.90)

[a] Employed ≥ 10 years in rubber or tire manufacturing, plastic production or processing, or pesticide production.

Table 2

Risk of urothelial cancer in diabetics relative to nondiabetics overall, and by sex, ethnicity, smoking status and stage.

	Number of cases		
	Diabetes	**No diabetes**	**RR[a] (95% CI)**
Overall	135	783	1.25 (1.04–1.50)
By sex			
Men	101	599	1.18 (0.96–1.47)
Women	34	184	1.48 (1.02–2.14)
By ethnicity			
Japanese American	38	239	1.07 (0.76–1.51)
White	30	286	1.38 (0.95–2.01)
Latino	22	106	1.03 (0.65–1.63)
African American	32	117	1.40 (0.94–2.07)
By smoking			
Never	26	181	1.13 (0.74–1.71)
Former smokers	86	412	1.31 (1.04–1.66)
Current smokers	23	190	1.15 (0.74–1.79)
By stage			
In situ and localized	105	632	1.23 (0.99–1.51)
Regional/distant	21	114	1.25 (0.78–2.00)

[a]Relative risk and 95% confidence interval [RR (95% CI)] for urothelial cancer associated with diabetes controlling for ethnicity and sex as strata variables and adjusting for smoking status, intensity and duration, and employment in a high risk industry, when not stratified by these variables.