Published in final edited form as:

Urol Oncol. 2014 January ; 32(1): . doi:10.1016/j.urolonc.2012.09.001.

Persistence of urothelial carcinoma of the bladder risk among former smokers: Results from a contemporary, prospective cohort study

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Abstract

Objectives—Cigarette smoking is a known risk factor for urothelial carcinoma (UC) of the bladder. However, the persistence of an increased risk for UC following smoking cessation is not well established. We assessed the risk of UC among former smokers using a recent, prospective cohort with a high proportion of former smokers.

Materials and methods—Study participants were members of the VITamins And Lifestyle cohort (VITAL), a group of 77,719 men and women between the ages of 50 and 76 years from western Washington State. Smoking history and other risk factors were obtained at the time of recruitment. The primary outcome was a new diagnosis of UC ($n = 385$), as determined through linkage to a population-based cancer registry.

Results and limitations—The cohort included 8% current and 44% former smokers, and among the UC cases, 15% were current and 60% former smokers. Both the current and former smoker had an increased risk of UC compared with never smokers (hazard ratio [HRs]: 3.81; 95% confidence intervals [CI] 2.71–5.35 and 2.0; 95% CI 1.55–2.58, respectively). Among former smokers, the risk of UC increased with the pack-years smoked and decreased with the years since quitting. When both the measures of smoking were considered together, the risk of UC was similar for long-term quitters and recent quitters for a given level of pack-years. For example, for those with pack-years of 22.5–37.5, the HR of UC was 1.91 (95% CI 1.17–3.11) for the distant quitters (> 23.5 y before baseline) and HR = 1.92 (95% CI 1.26–2.94) among the recent quitters. Limitations include the small number of cases at the extremes of smoking history and errors in self-reported smoking history.

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Conclusions—The risk of bladder cancer in former smokers remains elevated >32 years after quitting, even among those with moderate smoking histories. This argues that a history of smoking confers a lifelong increased risk of UC.

Keywords

Smoking; Urothelial carcinoma; Bladder; Smoking cessation

1. Introduction

Smoking is a known risk factor for urothelial carcinoma (UC) of the bladder, and several prospective cohorts have established a 2.5- to 4-fold increased risk of UC among smokers [1-5]. These same studies have also shown that the risk of UC tends to increase with increasing smoking intensity.

Despite the established associations between UC and smoking, several important questions remain. Prior studies have found that the risk of UC for former smokers remains elevated after quitting, but the relative contributions of the time since quitting and the smoking intensity are not clear [1-3,5]. A prior pooled analysis of case-control studies suggested that the risk remained elevated more than 24 years after quitting [6,7]. Another case-control study suggested that the risk of UC among former smokers may approach that of never smokers after more than 30 years, although this was for a small number of cases with an imprecise estimate [1]. Assessing the risk of UC and other malignancies in former smokers is important given that smoking prevalence has decreased greatly in both the United States, from 42.4% in 1965 to 20.6% in 2009, and the United Kingdom, from 45% in 1974 to 21% in 2009, whereas the number of former smokers has increased [8,9]. Studying a contemporary cohort composed mostly of never and former smokers is necessary to understand the current relationship of smoking and UC risk.

In this study, we investigated the persistence of increased UC risk following smoking cessation. We utilized a large, prospective cohort established in 2000 to examine the risk of UC among former smokers, including the effect of pack-years smoked and the time since quitting on the risk of UC.

2. Methods

2.1. Selection of study participants

Study participants are members of the VITamins And Lifestyle cohort (VITAL), a group of 77,719 men and women between the ages of 50 and 76 years living in a 13-county area of western Washington State. The study was approved by the institutional review board of the Fred Hutchinson Cancer Research Center. Methods of cohort recruitment, data collection and follow-up of outcomes have been described [10]. Briefly, cohort recruitment occurred from October 2000 to December 2002 by using a purchased commercial mailing list, which identified 364,418 individuals who were sent a 24-page self-administered questionnaire. Of the 79,300 questionnaires returned, 77,719 met the eligibility and the quality control checks. For the present analysis, we excluded 665 participants who reported a diagnosis of bladder cancer prior to entering the study or had missing data on prior bladder cancer. Six participants who developed nonurothelial histology bladder cancer (squamous cell carcinoma not otherwise specified, adenocarcinoma not otherwise specified or mucin-producing adenocarcinoma) were also excluded. Finally, those 615 participants who did not answer the smoking-history question were also excluded after initial case identification, leaving a total of 76,433 participants for analysis.

2.2. Baseline data collection

Baseline data were obtained from the 24-page self-administered questionnaire that included items on smoking history, dietary-supplement use, diet, medical history, personal characteristics, and cancer risk factors. Participants were asked if they were current or past cigarette smokers, the age they began smoking (14, 15–17, 18–21, 22–29, or 30), the number of cigarettes smoked per day (1–4, 5–14, 15–24, 25–35, 35–44, 45–54, and 55+), and the duration of smoking (1–4, 5–9, 10–19, 20–29, 30–39, and 40+ years). Years since quitting smoking was computed from the age at baseline, the age at which they began smoking and the number of years smoked.

2.3. Primary outcome, follow-up of subjects, and censored data

The primary outcome was defined as a new diagnosis of UC of the bladder. After completion of baseline data collection, participants were followed up for UC through December 31, 2008, by linking the cohort to the Seattle-Puget Sound Surveillance, Epidemiology and End Results (SEER) cancer registry. A total of 385 incident cases of UC were identified during the follow-up period.

For each subject, the end of follow-up was defined as the earliest of the following dates: the date of diagnosis of UC (0.50%), the date when the subject withdrew from the study (0.03%), the date when the subject moved out of the 13 counties of western Washington covered by Surveillance, Epidemiology and End Results (5.44%), the date of death (6.83%), or the date of last cohort follow-up, December 31, 2008 (87.21%). Deaths were ascertained by linkage to the Washington State death files and moves out of the area were monitored via the United States Post Office National Change of Address system and follow-up letters and phone calls to participants.

2.4. Statistical analyses

Hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) for UC in association with the smoking status, the pack-years smoked, and the time since quitting were obtained from Cox proportional hazard regression models using age as the time scale.

Subjects were grouped by quartile based on the pack-years smoked or the time since quitting. All regression models included variables for age, gender, race, education, and family history of UC, which were identified a priori as factors associated with the development of UC. Finally, persistence of UC risk was assessed by stratifying former smokers above and below the median time since quitting and comparing the quartiles of pack-years smoked with never smokers. Current smokers were excluded from all comparisons of former smokers to never smokers. Former smokers missing pack-year data ($n = 269$, 2 cases, and 267 controls) were excluded from analyses involving pack-year history. All statistical analyses were performed in STATA v11 (STATA CORP, College Station, TX).

3. Results

Our cohort included 36,373 persons who never smoked, 33,648 former smokers, and 6,412 current smokers. Among current and former smokers, the median pack-year history was 15.0 (interquartile range [IQR] 7–35) and 37.5 (IQR 22.5–47.3) years, respectively. The median time since quitting was 23.5 (IQR 14–32) years for former smokers. There were 385 patients of UC identified at last follow-up, 298 (77.5%) of which were male (Table 1).

Both current and former smokers had an increased risk of UC compared with never smokers, with HRs of 3.81 (95% CI 2.71–5.35, $P<0.001$) and 2.00 (95% CI 1.55–2.58, $P<0.001$), respectively (Table 2).

Among former smokers, all quartiles of pack-years had an increased risk of UC, with a significant dose-response trend ($P<0.001$) (Table 3). For those in the lowest quartile, less than 7.5 pack-years, the HR was 1.46 (95% CI 1.02–2.09) whereas those in the highest quartile, 37.5 pack-years and above, had an HR of 2.77 (95% CI 2.00–3.85) (Table 3). Risk of UC decreased with the increased time since quitting smoking but remained elevated for those who had the longest time since quitting. Compared with never smokers, those who quit in the distant past had an HR of 1.50 (1.07–2.11), whereas recent quitters had an HR of 2.52 (95% CI from 1.79–3.53).

Because recent quitters would have, on average, accumulated more pack-years than those who quit in the distant past, we stratified analyses of UC associated with pack-years of smoking by the median time since quitting smoking (Table 4). The positive association of cumulative amount smoked and UC risk persisted in those who had quit more than 23.5 years ago. Moreover, the risk of UC appeared to be similar for long-term quitters and recent quitters for a given level of pack-years of smoking.

4. Discussion

Using a large contemporary, prospective cohort we confirmed previous findings of the risk of UC associated with smoking, while showing that the risk of UC persists even >32 years after quitting. These findings are important considering the increasing prevalence of former smokers in the United States and Europe. In contrast to other studies, our study included many more former (44%) than current smokers (8%).

Several previous studies have reported on the association between smoking history and UC. One prior large study conducted in the United States by Alberg et al. used 2 separate cohorts from 1963 and 1975 and found a 3-fold increased risk of UC with active smoking [4]. However, the results for former smokers were inconsistent, with no elevated risk in the 1963 cohort and a 2.5-fold increased risk in the 1975 cohort. This was possibly due to a low number of former smokers in that study (15% and 23% of the cohorts in 1963 and 1975, respectively). Two recent cohort studies have updated the risk of UC associated with smoking, one a large, prospective European cohort (EPIC) and the other a large, prospective cohort based in the United States (NIH-AARP) [3,5]. These 2 studies reported nearly identical risk estimates of UC for former smokers (HRs: 2.25 and 2.22, respectively) and current smokers (HRs: 3.96 and 4.06, respectively) compared with never smokers. We found a similar risk of UC among current smokers (HR: 3.81, 95% CI 2.71–5.35) and former smokers (HR: 2.00, 95% CI 1.55–2.58).

The relationship between the time since quitting smoking and the risk of UC is important considering that the number of former smokers exceeds the number of current smokers in the United States [11]. A prior meta-analysis by Brennan et al. of 11 case-control studies prior to 2000 found evidence that the odds of UC in male former smokers remained nearly 2-fold higher up to 24 years after quitting [7]. More recently, Bjerregaard et al. found that the UC risk decreased with the time since quitting but even those who had quit >21 years ago still had a 1.5-fold increased risk compared with never smokers [3]. Zeegers et al. found that after 30 years the risk in former smokers approached that of never smokers, although there were few cases among those who quit more than 30 years ago [1]. The findings in our current study suggest that even more than 32 years after quitting, the risk of UC in former smokers remains 1.5 times higher than that in never smokers (95% CI 1.07–2.11). We also

show even those with moderate smoking histories had a higher risk of UC than never smokers. Furthermore, when pack-years of smoking are taken into account, the risk of UC appears to be similar for long-term quitters and recent quitters. The NIH-AARP study reported that those who quit more than 10 years ago had a lower risk of UC than those who quit more recently when stratified by cigarettes smoked per day, [5] but that does not take into account that years of smoking is longer on average for those who quit more recently.

The best characterized mechanism by which smoking initiates carcinogenesis is through the formation of DNA adducts. However, studies comparing adduct levels in bladder tissue between former and never smokers have not demonstrated significant differences [12,13]. More recently, changes in DNA methylation have been observed as contributors to bladder carcinogenesis and are more common among former smokers with UC than nonsmokers with UC [14,15]. However, hypomethylation among former smokers who do not have UC has not been demonstrated [16]. Thus, although the persistence of UC risk among former smokers is clear, the underlying mechanism is not.

There are limitations of our study. First, this cohort was recruited to study the effects of nutrition and vitamin supplementation on cancer risk. People who are more health conscious may have been more likely to respond, which may partially explain the low level of smoking in this cohort. The prevalence of smoking in the United States in 2007 was 20%, whereas our cohort only had 8% [9]. Further, our cohort comes from the State of Washington that, in 2006, had the eighth lowest smoking prevalence among all the states [17]. However, this is unlikely to lead to bias the estimates of risk of UC associated with smoking history, because participants cannot decide to join the cohort based jointly on smoking and future UC occurrence. Second, smoking history was ascertained by recall and self-report. Although a prior study based in the United States estimated a low rate (1.4%) of smoking among self-reported non-smokers, it likely that some participants did not accurately report their smoking status or history [18]. As this error would be nondifferential by case status in a prospective study, this would have led to attenuation of the risk estimates. It is also likely that some former smokers resumed smoking after the time of the survey whereas others may have quit smoking. Depending on how often this happens, this could decrease the observed difference in risk between current smokers and former smokers. Finally, only 385 cases of bladder cancer occurred over the course of 7 years of follow-up. When the results were stratified by the time since quitting and the pack-year history, there were few events in some groups. This led to low precision in some HR estimates.

In conclusion, using a large, contemporary cohort with a high number of former smokers, we found that the risk of bladder cancer in former smoker remains elevated long after quitting. The risk was primarily a function of pack-years smoked, but was elevated even for those with moderate smoking histories. Based on this and the prior reports of UC risk in former smokers, we were unable to identify a point at which UC risk in former smokers is the same as that in never smokers. This argues that a history of smoking should continue to be considered a strong risk factor for UC throughout a person's life.

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Table 1

Urothelial carcinoma of the bladder cases and controls by baseline participant characteristics and smoking status for western Washington State, 2000–2008

Characteristic	Cases (378)	%	Noncases (76,055)	%
Demographic Variables				
Sex				
Male	292	77.3	36,161	47.6
Female	86	22.7	39,894	52.4
Age at baseline, y				
50–54	34	9.0	17,775	23.4
55–59	44	11.6	17,339	22.8
60–64	51	13.5	13,872	18.2
65–69	92	24.4	12,467	16.4
70–76	157	41.5	14,602	19.2
Race/ethnicity				
White	356	94.2	69,939	92.0
Black	4	1.0	964	1.3
Other	18	4.8	5,152	6.7
Education				
High school or less	97	25.7	15,194	20.2
Some college/technical School	130	34.4	28,891	38.3
College graduate	86	22.8	18,465	24.5
Advanced degree	63	16.7	12,808	16.6
Family history of bladder cancer				
No	361	95.5	72,948	95.9
Yes	11	2.9	2,179	2.9
Smoking variables				
Smoking status				
Never	92	24.3	36,281	47.7
Former	228	60.3	33,420	43.9
Current	58	15.3	6,354	8.4
Pack years ^a				
Never	92	24.5	36,281	47.9
7.5	48	12.8	11,983	15.8
>7.5–22.5	60	16.0	9,337	12.3
>22.5–37.5	64	17.0	9,064	12.0
> 7.5	112	30.0	9,096	12.0
Years since quitting ^b				
Never	92	28.9	36,281	52.3
>32	56	17.6	8,208	11.8
>23.5–32	59	18.6	8,267	11.9

Characteristic	Cases (378)	%	Noncases (76,055)	%
>14–23.5	52	16.4	8,323	12.0
14	59	18.6	8,297	12.0

^aNever smokers excluded.

^bCurrent smokers and never smokers excluded.

Table 2Adjusted^a risk of urothelial carcinoma of the bladder by smoking status

	Cases (<i>n</i>)	Noncases (<i>n</i>)	HR (95% CI)	<i>P</i> -value
Never smoked	92	36,373	1.00 (referent)	
Former smoker	228	33,648	2.00 (1.55–2.58)	<0.001
Current smoker	58	6,412	3.81 (2.71–5.35)	<0.001

^a Adjusted for age, race, gender, education, and family history of urothelial cancer.

Table 3

Adjusted^a risk of urothelial carcinoma of the bladder by pack-years and years since quitting among former smokers

Smoking variables	Cases (n)	Noncases (n)	HR (95% CI)	P-value ^b
Pack-years smoked ^c				
Never smoked	92	36,281	1.00 (referent)	<0.001
<7.5	46	11,640	1.46 (1.02–2.09)	
7.5–<22.5	55	8,002	2.06 (1.46–2.90)	
22.5–<37.5	53	7,668	1.91 (1.34–2.71)	
37.5 and above	72	6,069	2.77 (2.00–3.85)	
Years since quitting ^d				
Never smoked	92	36,281	1.00 (referent)	<0.001
32 and above	56	8,208	1.50 (1.07–2.11)	
23.5–<32	59	8,267	2.16 (1.54–3.03)	
14–<23.5	52	8,323	2.10 (1.42–2.86)	
<14	59	8,297	2.52 (1.79–3.53)	

^a Adjusted for age, race, gender, education, and family history of urothelial cancer.

^b P-value for trend.

^c Excludes those who did not answer the smoking-duration question.

^d Excludes those who did not provide a time since quitting.

Adjusted^a risk of urothelial carcinoma of the bladder by pack-years of smoking, stratified by years since quitting, among former smokers

Table 4

Pack-years	Years since quitting					
	<23.5 y			23.5 y		
	Cases (n)	Noncases (n)	HR (95% CI)	Cases (n)	Noncases (n)	HR (95% CI)
Never smoked	92	36,281	1.00 (referent)	92	36,281	1.00 (referent)
<7.5	2	1,580	^b NA	44	9,974	1.51 (1.05–2.17)
7.5–22.5	15	3,876	1.75 (1.01–3.04)	40	4,047	2.23 (1.51–3.29)
22.5–37.5	30	5,677	1.92 (1.26–2.94)	23	1,900	1.91 (1.17–3.11)
>37.5	64	5,433	2.74 (1.94–3.86)	8	494	^b NA
			^c P 0.001			^c P 0.001

^a Adjusted for age, race, gender, education, and family history of urothelial cancer.

^b Too few cases to report HR.

^c P-value is for trend with increasing pack-years.