

Original article

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.

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. © 2014 Elsevier Inc. All rights reserved.

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

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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 (STACORP, 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

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