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Association between smoking and risk of bladder cancer among men and women

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Abstract

Context—Previous studies indicate that the population attributable risk of bladder cancer for tobacco smoking is 50–65% in men and 20–30% in women and that current cigarette smoking triples bladder cancer risk relative to never smoking. Over the last 30 years, incidence rates have remained stable in the United States (men: 123.8/100,000 person-years to 142.2/100,000 person-years; women: 32.5/100,000 person-years to 33.2/100,000 person-years), yet changing smoking prevalence and cigarette composition warrant revisiting risk estimates for smoking and bladder cancer in more recent data.

Objective—To evaluate the association between tobacco smoking and bladder cancer.

Design, Setting, and Participants—Men (n=281,394) and women (n=186,134) of the NIH-AARP cohort completed a lifestyle questionnaire and were followed from 1995 through Dec 31, 2006. Previous prospective cohort studies of smoking and incident bladder cancer were identified by systematic review and pooled using fixed effects models with heterogeneity assessed by I^2.

Main outcome measures—Hazard ratios (HR), population attributable risks, and number needed to harm (NNH).

Results—During 4,518,938 years of follow-up, incident bladder cancer occurred in 3,896 men (144.0/100,000 person-years) and 627 women (34.5/100,000 person-years). Former smokers (119.8/100,000 person-years, HR: 2.22, 95%CI: 2.03–2.44, NNH: 1,250) and current smokers

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(177.3/100,000 person-years, HR: 4.06, 95%CI: 3.66–4.50; NNH: 727) had higher risks of bladder cancer than never smokers (39.8/100,000 person-years). In contrast, the summary risk estimate for current smoking in seven previous studies (initiated from 1963–1987) was 2.94 (95%CI: 2.45–3.54; I^2=0.0%). The population attributable risk for ever smoking in our study was 0.50 (95%CI: 0.45–0.54) in men and 0.52 (95%CI: 0.45–0.59) in women.

Conclusions—Compared to a pooled estimate of US data from cohorts initiated between 1963 and 1987, relative risks for smoking in the more recent NIH-AARP cohort were higher, with population attributable risks for women comparable to those for men.

Introduction

More than 350,000 individuals are diagnosed with incident bladder cancer per year worldwide,[1] including more than 70,000 per year in the United States.[2] In data from Surveillance, Epidemiology and End Results (SEER) Program, incidence rates in Whites aged 50 plus have remained stable over the past 30 years (1976–2006), from 123.8/100,000 person-years to 142.2/100,000 person-years in men and from 32.5/100,000 person-years to 33.2/100,000 person-years in women; similar patterns are seen in other ethnic and racial groups.[3]

First evaluated in the 1950s, tobacco smoking is the best established risk factor for bladder cancer in both men and women.[4,5] Although rates of bladder cancer have remained stable over the past thirty years, the prevalence of cigarette smoking in the United States has substantially decreased over the same time period.[6]

Typically, risk estimates for current smokers have been about three in previous studies.[5,7] Yet the composition of cigarettes has changed over the past 50 years, leading both to a reduction in tar and nicotine concentrations in cigarette smoke,[8] but also to an apparent increase in the concentration of specific carcinogens including β-napthylamine, a known bladder carcinogen, and tobacco- specific nitrosamines.[9] Concurrent with these changes in the constituents of cigarette smoke, epidemiologic studies have observed higher relative risks associated with cigarette smoking for lung cancer.[10] A recent report from the New England Bladder Study, a large population-based case-control study, suggests that the strength of the cigarette smoking-bladder cancer association may also have increased.[11] In this report, the authors compared the odds ratio for current smokers relative to never smokers in three similar population-based case-control studies performed in New Hampshire in 1994–1998, 1998–2001, and 2001–2004. Over the course of the three studies, the odds ratio associated with current smoking increased from 2.9 (95%CI: 2.0–4.2) to 4.2 (95%CI: 2.8–6.3) to 5.5 (95%CI: 3.5–8.9). These provocative results suggest that changing cigarette composition over time may be associated with increased bladder cancer risk, analogous to results previously documented for lung cancer. Stronger associations between smoking and bladder cancer could potentially offset the decreased prevalence of smoking in the US population and contribute to the stability of the bladder cancer incidence rates over the past 30 years. However, these findings need replication, particularly in prospective cohort studies.

Population attributable risks (PAR) for tobacco smoking have been estimated to be 50–65% in men and 20–30% in women.[5,12–15] Yet, these estimates were based on studies conducted in populations and during time periods where the prevalence of smoking was higher in men than in women. Currently, in the United States and in many other countries, the prevalence of smoking is similar in men and women.[16,17]

Our purpose was to estimate the strength of the association between tobacco smoking and bladder cancer and the PARs for smoking among men and women in the large, prospective NIH-AARP Diet and Health study, initiated in 1995 with follow-up through the end of 2006.

Materials and Methods

The NIH-AARP Diet and Health study has been described previously.[18] Briefly, a questionnaire was mailed in 1995–1996 to 3.5 million AARP members 50–71 years of age who resided in eight states (California, Florida, Georgia, Louisiana, Michigan New Jersey, North Carolina, and Pennsylvania). Of 617,119 returned questionnaires, 566,401 were completed in satisfactory detail. The NIH-AARP Diet and Health Study was reviewed and approved by the Special Studies Institutional Review Board of the US National Cancer Institute (NCI) and all participants gave informed consent by virtue of completing and returning the questionnaire.

Cohort follow-up

Addresses for cohort members were updated annually in response to participant change of address requests and by matching cohort participants to the United States Post Office National Change of Address database. Vital status was obtained by linkage to the Social Security Administration Death Master File and response to mailings. Follow-up time started the date the questionnaire was returned (beginning October 25, 1995) and accumulated until diagnosis of bladder cancer, a move out of the catchment area, date of death, or December 31, 2006.

Identification of bladder cancers

We identified incident bladder cancers by linking the NIH-AARP cohort with the cancer registry databases of ten states (eight baseline states plus Arizona and Texas). In a validation study, this approach identified approximately 90% of cancers.[19] Bladder cancer cases had an International Classification of Disease for Oncology[20] site code of C67.0–C67.9 and a transitional cell (urothelial) morphology (ICD codes 8120, 8122, 8123, or 8130).

Exposure Assessment

The baseline questionnaire assessed tobacco use, alcohol intake, demographics, physical activity, and intake of 124 food items. Race/ethnicity (Non-Hispanic white, Non-Hispanic black, Hispanic, Asian, Pacific Islander, or Native American) was assessed by self-report and was collected in order to study whether the association of cancer risk factors differed by racial or ethnic group. Assessment of tobacco use via questionnaire has shown high reproducibility (r=0.94) and validity (r=0.92 for women and r=0.90 for men relative to serum cotinine levels) in previous methodologic studies.[21,22] Participants were considered ever cigarette smokers if they had smoked more than 100 cigarettes during their lifetimes. In responding to the questionnaire, ever smokers recorded their typical cigarette smoking intensity using six categories of cigarettes per day (1–10, 11–20, 21–30, 31–40, 41–60, and 61 cigarettes or more; former smokers reported years of smoking cessation using four categories (stopped within the last year, stopped 1–4 years ago, stopped 5–9 years ago, and stopped 10 or more years ago). We considered those who had quit more than one year before baseline as former cigarette smokers. A separate question assessed whether participants had regularly smoked pipes or cigars for one year or longer.

Statistical Methods

We used a significance level of 0.05 and all conducted statistical tests were two sided.

We completed all NIH-AARP analyses using SAS version 9.1. We calculated age-standardized incidence rates and 95% confidence intervals using five-year age bands standardized to the entire NIH-AARP Diet and Health study population.[23] The number needed to harm (NNH) was calculated from age-standardized incidence rates.

For relative risks, hazard ratios (HR) and 95% confidence intervals (CI) were calculated using Cox proportional hazards regression.[24] Risk estimates were adjusted for age, education, ethnicity, and pipe or cigar use. Additional adjustment for other possible confounders such as alcohol, aspirin and ibuprofen nonsteroidal anti-inflammatory drugs, body mass index, physical activity, self-reported health, or intake of fruit, vegetables, meat, or total energy did not alter risk estimates. For the less than 3% of the cohort that was missing data for a particular covariate, a separate indicator variable for missing was included in the models.

We tested the proportional hazards assumption by including an interaction term for follow-up time and cigarette use in the Cox models and we found no statistically significant deviations.

Linear trend tests across categories of cigarette smoking were conducted by assigning participants their appropriate category of cigarette smoking and entering this variable as a continuous term in the regression model. P-values were then obtained from the Wald test.

We used the method of Bruzzi et al[25] to calculate population attributable risks from multivariate-adjusted beta-coefficients for ever smoking. The delta method was used to estimate the variance in order to estimate the 95% confidence intervals for the PAR estimates.[26]

Systematic review of previous prospective cohort studies

We identified previous US prospective cohort studies that assessed cigarette smoking at baseline and examined the association of current smoking with subsequent bladder cancer incidence by using the following search terms in PubMed and Embase ((tobacco OR smok* OR cig*) AND (cancer OR carcinoma OR neoplas*) AND (bladder OR urinary tract OR urolog* OR urothelial) AND (cohort OR prospective)) (Supplementary Figure 1). Our search was performed on June 28, 2011 and included all publications in the databases published until then. We did not restrict our search by language. After excluding duplicates, our search yielded 843 articles. Titles and abstracts were reviewed and we excluded studies conducted in populations outside of the United States or that lacked data on incident bladder cancer, leaving 60 studies. We reviewed all 60 published manuscripts, excluding one published abstract, studies conducted outside the United States, reviews, cross-sectional studies, studies of bladder cancer mortality, studies with overlapping results, and studies lacking risk estimates for current versus never smoking. After these exclusions, six publications remained which provided data from seven cohorts. No further publications were identified upon reviewing the references of these six remaining articles. We did not assess study quality and instead chose to include all identified studies in our meta-analysis.

From each article, we extracted data on the authors and year of publication, cohort name, participant sex, mean age, number of never smoking cases and cohort participants, number of current smoking cases and cohort participants, typical amount of cigarettes smoked per day among current smokers, and the relative risk for current, relative to never, smoking. We extracted maximally adjusted risk estimates. In studies which lacked one or more extraction variables, we sought this data in previous cohort publications. We did not contact study authors. Two co-authors, NDF and CCA, reviewed each publication to ensure that the data extraction was accurate.

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We used STATA 11.0 to perform meta-analysis. Heterogeneity between studies was assessed by the I^2 statistic and the Cochran Q test.[27] Summary relative risks and 95% confidence intervals were calculated using fixed-effects models (Mantel–Haenszel method). We examined possible publication bias using both Begg and Mazudmar's *P*-value for rank correlation[28] and Egger's weighted regression method.[29]

Additional analyses were performed including data from previously published studies together with NIH-AARP. Possible heterogeneity across studies was examined using the I^2 statistic and the Cochran Q test.

Results

Participants with cancer (except non-melanoma skin cancer) at baseline (51,234), proxy respondents (15,760), those who died or who were diagnosed with cancer on the first day of follow-up (13), or failed to provide information about cigarette use (19,329) or cigar and pipe use (12,537) were excluded, resulting in an analytic cohort of 281,394 men and 186,134 women. Men and women entered the study at similar ages, but men had more formal education, drank more alcohol, ate less fruit and vegetables, and were more likely to have ever smoked cigarettes, pipes, or cigars and to have smoked more than 40 cigarettes per day than women. But, a higher proportion of women than men were current smokers. The median age of smoking initiation was 17 in the subset of the cohort (118,557 men and 72,030 women) who returned a follow-up questionnaire in September 2004 (Table 1).

Over the course of 4,518,938 years of follow-up, 3,896 men and 627 women were newly diagnosed with bladder cancer. Overall incidence rates were 144.0/100,000 person-years (95%CI: 139.4–148.5) in men and 34.5/100,000 person-years (95%CI: 31.8–37.3) in women. Cigarette smoking was a strong risk factor for bladder cancer in both sexes (Table 2). Relative to never smokers (men: 69.8/100,000 person-years; women: 16.1/100,000 person-years), former and current smokers had elevated risk of bladder cancer in both men (former, 154.6/100,000 person-years, HR: 2.14 (95%CI: 1.92–2.37), NNH: 1,179; current, 276.4/100,000 person-years, HR: 3.89 (95%CI: 3.46–4.37), NNH: 484) and women (former, 40.7/100,000 person-years, HR: 2.52 (95%CI: 2.05–3.10), NNH: 4,065; current, 73.6/100,000 person-years, HR: 4.65 (95%CI: 3.73–5.79), NNH: 1,739). The combined risk estimates including both sexes were 2.22 (95%CI: 2.03–2.44) for former smokers (119.8/100,000 person-years; NNH: 1,250: 95%CI: 1,171–1,343) and 4.06 (95%CI: 3.66–4.50) for current smokers (177.3/100,000 person-years; NNH: 727, relative to never smokers (39.8/100,000 person-years).

As in previous studies, smoking cessation was associated with reduced bladder cancer risk in both sexes. Participants who quit ≥ 10 years before baseline had lower incidence rates of bladder cancer than those who quit 1–5 or 5–<10 years before baseline. Nevertheless, relative to never smokers, risks remained elevated for men and women who quit even ≥10 years before baseline. Pipe and cigar use was also associated with risk in men (HR: 1.29, 95%CI: 1.07–1.56; 92.5/100,000 person-years vs. 69.8/100,000 person-years; NNH: 4,405. Too few women in the cohort smoked pipes or cigars to be analyzed.

Overall, men had 3.71 (95%CI: 3.39–4.06; 144.0/100,000 person-years vs. 34.5/100,000 person-years) times the risk of women for bladder cancer (Table 3). Among stratum of cigarette smoking, risks for men relative to women ranged from 1.99 to 6.62. Elevated rates persisted in never-smokers where men (69.8/100,000 person-years) had 4.07 (95%CI: 3.34–4.97) times the bladder cancer risk of never-smoking women (16.1/100,000 person-years).

The PAR for ever smoking in the NIH-AARP study was similar in men (0.50, 95%CI: 0.45–0.54) and women (0.52, 95%CI: 0.45–0.59).

Next, we performed a systematic review and meta-analysis of previously published US prospective cohort studies of current cigarette smoking and incident bladder cancer (Supplementary Figure 1). We identified data from the seven cohorts (Table 4). In these cohorts initiated between 1963 and 1987, the summary risk estimate was 2.94 (95%CI: 2.45–3.54) with an I^2 of 0.0% and the Cochran Q test p-value for between study heterogeneity was 0.554. We observed no evidence for publication bias by either Egger's weighted regression (p-value =0.315) or Begg and Mazumdar's rank correlation method (p-value =0.293).

Addition of risk estimates from the NIH-AARP study to the meta-analysis raised the summary risk estimate to 3.75 (3.43–4.10) and increased the I^2 to 48.7%, such that the Cochran Q test p-value for between study heterogeneity became statistically significant (p=0.049).

Comment

In the NIH-AARP prospective cohort study, cigarette smoking was strongly associated with bladder cancer risk in both men and women and ever smoking explained a similar proportion of bladder cancer in both sexes, with PARs of 50% in men and 52% in women.

With follow-up occurring between 1995 and 2006, current smoking was associated with a relative risk of 4.06 (95%CI: 3.66–4.50) in men and women combined. This risk estimate for current smoking is broadly similar to those observed in New Hampshire case-control data for cases diagnosed in 1998–2001 and 2002–2004 and higher than those for cases diagnosed from 1994–1998. The 1994–1998 cases had an odds ratio of 2.9 (95%CI: 2.0–4.2), whereas the cases diagnosed from 1998–2001 had an odds ratio of 4.2 (95%CI: 2.8–6.3) and the cases diagnosed from 2002–2004 had an odds ratio of 5.5 (95%CI: 3.5–8.9).[11] Previously published US prospective cohort studies of cigarette smoking and incident bladder cancer risk in men and women were initiated between 1963 and 1987. The summary estimate from these seven cohorts was 2.94 (95%CI: 2.45–3.54), which is significantly lower than that observed in our current study. These observations parallel those previously reported for lung cancer, where changes in cigarette design have been linked to stronger associations with cigarette smoking.[10] Changes in the constituents of cigarette smoke, including apparent increased concentrations of β-napthylamine, a known bladder carcinogen, and tobacco-specific nitrosamines[9], may have strengthened the smoking/bladder cancer association as well. Alternatively, differences between the present and past studies could have been due to chance, although a recently published meeting abstract from the VITamins And Lifestyle Study also indicated a HR of 4 (95% CI 2.9–5.8) for current smoking versus never smoking for incident bladder cancer.[30]

Although our data suggest that the association of cigarette smoking with bladder cancer has strengthened, incidence rates have stayed largely constant over this same time period. Yet cigarette composition is just one of the smoking-related changes occurring during this time. Substantial reductions in the prevalence of cigarette smoking have also occurred.[17] Our results, and those of the New England Bladder Cancer Study, suggest that the strengthening of the smoking-related relative risks, perhaps due to changing cigarette composition, may have offset the effect of declining smoking prevalence, at least to some extent, contributing to relatively stable incidence rates of bladder cancer over the past thirty years. Future work is needed to investigate this hypothesis.

In the NIH-AARP cohort, where the prevalence of smoking is generally similar in men and women, as is seen in the overall United States,[16,17] the PAR for smoking was about 50% in both sexes. Previous studies have found PARs of 50–65% in men and 20–30% in women,[5,12–15] but were conducted in populations where the prevalence of smoking in women was considerably lower than in men.[31] In our study cohort and in the general US population,[16,17] however, the prevalence of smoking is similar in men and women. This is the first report to demonstrate that the increased prevalence of smoking in US women has led to an increased PAR for smoking, such that the PARs for smoking and bladder cancer are now similar in US men and women.

In addition to bladder cancer, tobacco smoking is strongly associated with increased risk of lung cancer.[32] Incidence rates of lung cancer, like for bladder cancer, are higher in men than women worldwide.[1] Historically higher rates of tobacco smoking in men relative to women likely explain most of the male excess in lung cancer cases. As the prevalence of tobacco smoking in women has increased,[33] incidence rates of lung cancer in men and women have converged in many countries, including the United States.[16,33,34] Furthermore, we demonstrated similar incidence rates of lung cancer in the men and women of the NIH-AARP cohort; both among men and women who smoked similar amounts and among never smokers.[35]

In contrast to the lung, incidence rates of bladder cancer have not converged in men and women,[7] even in countries such as the United States where men and women now smoke similar amounts.[34] In the current study, we observed consistently higher incidence rates of bladder cancer in men than women, both among individuals who smoked similar amounts and among never smokers. Our results are consistent with the National Bladder Cancer Study, a population-based case-control study conducted in 1978.[15] In this study, as in ours, risk of bladder cancer remained higher in male versus female never smokers. Although differences in the prevalence of smoking are likely an important explanation for the male excess of bladder cancer in the many parts of the world where cigarette smoking is substantially more common in men than women,[36,37] our results and those of the National Bladder Cancer Study[15] suggest that differences in smoking use do not completely explain higher incidence rates of bladder cancer in US men.[2] Higher incidence rates in men could also reflect occupational exposures; as men, in general, are more likely than women to work in specific occupations that have been traditionally associated with bladder cancer risk, such aromatic amine-manufacturing worker, leather worker, painter, truck driver, machinist, and aluminum worker.[5,38–40] We lacked assessment of occupation in the current study; however, bladder cancer risk among men in the National Bladder Cancer Study was attenuated after adjustment for occupational exposures, yet remained elevated relative to women.[15] Alternatively, physiologic differences between men and women, such as differences in the levels of sex hormones, could contribute to higher rates in men. Several recent studies provide evidence for associations between menstrual and reproductive factors with bladder cancer,[41–43] and this is an active area of investigation.

Strengths of our study include assessment of smoking use before cancer diagnosis, very large number of participants and incident bladder cancers, and presentation of both incidence rates (absolute risks) and relative risks. Several limitations should be noted. We lacked information about the age at smoking initiation for a majority of cohort participants and so couldn’t calculate smoking duration or pack-years. Among the subset of cohort participants (118,557 men and 72,030 women) returning a follow-up questionnaire in 2004, the median age at smoking initiation was 17 years in both men and women. In addition, smoking status was assessed only at baseline and was not updated over the course of follow-up. As a number of participants probably quit during follow-up, risk estimates for current smoking in our study are likely to be attenuated. Lastly, our results may not apply to other populations, particularly those in other countries that may differ in smoking prevalence and cigarette composition.

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Conclusions

Tobacco smoking was a strong risk factor for bladder cancer, with PARs of approximately 50% in both men and women. We found higher risk estimates for current cigarette smoking relative to never smoking in the NIH-AARP cohort, initiated in 1995, than were reported in previous publications from cohorts initiated between 1963 and 1987. These results support the hypothesis that the risk of bladder cancer associated with cigarette smoking has increased with time in the United States, perhaps a reflection of changing cigarette composition. Prevention efforts should continue to focus on reducing the prevalence of cigarette smoking.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Cancer incidence data from Arizona was collected by the Arizona Cancer Registry; from Georgia by the Georgia Center for Cancer Statistics; from California by the California Department of Health Services, Cancer Surveillance Section; from Michigan by the Michigan Cancer Surveillance Program; from Florida by the Florida Cancer Data System under contract to the Department of Health; from Louisiana by the Louisiana Tumor Registry; from New Jersey by the New Jersey State Cancer Registry; from North Carolina by the North Carolina Central Cancer Registry; from Pennsylvania by the Division of Health Statistics and Research, Pennsylvania Department of Health; from Texas by the Texas Cancer Registry. The views expressed herein are solely those of the authors and do not necessarily reflect those of the Cancer registries or contractors. The Pennsylvania Department of Health specifically disclaims responsibility for any analyses, interpretations, or conclusions.

We are indebted to the participants of the NIH-AARP Diet and Health Study for their outstanding cooperation. This paper is dedicated to the memory of Arthur Schatzkin.

Table 1

Characteristics of the NIH-AARP cohort by sex.

Characteristic*	Men	Women
Participants, No.	281,394	186, 134
Bladder cancers, No.	3,896	627
Age at entry into the cohort, years, Median (IQR)	62.7 (57.8–66.7)	62.3 (57.5–66.4)
Alcohol intake, No. (%)		
0 drinks/day	57,680 (20.6)	54,236 (29.3)
≤ – < 1 drinks/day	139,843 (49.8)	107,021 (57.7)
1 – ≤ 3 drinks/day	51,900 (18.5)	19,044 (10.3)
> 3 drinks/day	31,149 (11.1)	5,152 (2.8)
Body mass index, kg/m^2, Median (IQR)	26.6 (24.4–29.4)	25.8 (22.9–29.6)
Education, No. (%)		
Less than high school	16, 274 (5.9)	11, 403 (6.3)
12 years (completed high school)	43, 866 (16.0)	47, 402 (26.3)
Some post-high school training	89, 046 (32.4)	66, 284 (36.7)
Completed college	60, 812 (22.2)	27, 465 (15.2)
Completed graduate school	64, 447 (23.5)	27, 852 (15.4)
Ethnicity, No. (%)		
Non-Hispanic white	260,903 (93.7)	166,590 (90.7)
Non-Hispanic black	7,605 (2.7)	10,573 (5.8)
Hispanic	5,319 (1.9)	3,537 (1.9)
Asian/ Pacific Islander/ Native American	4,777 (1.7)	2,941 (1.6)
Fruit consumption, Servings per day, Median (IQR)	1.3 (0.8–2.1)	1.7 (1.0–2.5)
Vegetable consumption, Servings per day, Median (IQR)	1.9 (1.4–2.5)	2.2 (1.6–3.1)
Total daily energy intake, kcal, Median (IQR)	1,870 (1,435–2,428)	1,461 (1,119–1,898)
Cigarette smoking status, No. (%)		
Never	84,052 (29.9)	82,102 (44.1)
Former	161,435 (57.4)	72,086 (38.7)
Current	35,907 (12.8)	31,946 (17.2)
Usual number of cigarettes smoked per day (current and former), No. (%)		
1–10	39,353 (14.0)	37,388 (20.1)
11–20	62,773 (22.3)	35,362 (19.0)
21–30	42,664 (15.2)	17,177 (9.2)
31–40	28,760 (10.2)	8,883 (4.8)
> 40	23,792 (8.5)	5,222 (2.8)

Characteristic*	Men	Women
Age started smoking†, years, Median (IQR)	17, 13–22	17, 17–22
Years since quitting smoking (Among former smokers), No. (%)		
Stopped 10 or more years ago	128,542 (45.7)	50,583 (27.2)
Stopped 5–9 years ago	21,224 (7.5)	13,195 (7.1)
Stopped 1–4 years ago	11,669 (4.2)	8,308 (4.5)
Ever regularly smoked pipes or cigars (Yes), No. (%)	81, 056 (28.8)	802 (0.4)

*Categories may not add up to 467,528 persons because of missing data.

†Available for a subset of the cohort, 118,557 men and 72,030 women who returned a follow-up questionnaire in 2004.

Table 2

Incidence rates and hazard ratios (95% CIs) for cigarette smoking and bladder cancer by sex

	Men				Women			
Category	**Person-years**	**N**	**Age-standardized incidence rates/10^5 person-years (95% CI)**	**Multivariate adjusted HR* (95% CI)**	**Person-years**	**N**	**Age-standardized incidence rates/10^5 person-years (95% CI)**	**Multivariate adjusted HR* (95% CI)**
Never smoked cigarettes, pipes, or cigars	677,607	461	69.8 (63.4–76.1)	1.00 (ref)	821,064	133	16.1 (13.4–18.8)	1.00 (ref)
Never smoked cigarettes but smoked pipes or cigars	148,810	143	92.5 (77.3–107.7)	1.29 (1.07–1.56)	635	0	---	---
Former smoker (overall)†	1,540,789	2,483	154.6 (148.5–160.7)	2.14 (1.92–2.37)	70,595	288	40.7 (36.0–45.5)	2.52 (2.05–3.10)
Stopped ≥ 10 years ago	1,237,120	1850	140.2 (133.8–146.7)	1.93 (1.73–2.14)	499,493	171	33.6 (28.6–38.6)	2.08 (1.65–2.61)
Stopped 5–<10 years ago	197,325	394	206.9 (186.4–227.4)	2.85 (2.49–3.27)	127,140	69	55.7 (42.5–68.9)	3.49 (2.61–4.67)
Stopped 1–5 years ago	106,344	239	243.3 (212.2–274.4)	3.32 (2.84–3.89)	79,292	48	65.2 (46.7–83.7)	3.97 (2.85–5.53)
1–10 cigarettes/day	314,144	309	96.6 (85.8–107.3)	1.33 (1.15–1.55)	273,297	80	29.4 (22.9–35.8)	1.80 (1.36–2.38)
11–20 cigarettes/day	476,611	709	142.3 (131.8–152.8)	1.90 (1.68–2.15)	214,073	88	41.2 (32.6–49.8)	2.50 (1.91–3.27)
21–30 cigarettes/day	324,709	596	180.4 (165.9–194.9)	2.40 (2.11–2.72)	110,881	66	61.1 (46.3–75.9)	3.75 (2.78–5.04)
31–40 cigarettes/day	222,928	448	197.4 (179.1–215.7)	2.62 (2.29–2.99)	63,451	29	46.8 (29.7–63.9)	2.86 (1.91–4.28)
> 40 cigarettes/day	202,397	421	205.7 (186.1–225.4)	2.71 (2.36–3.10)	44,223	25	60.4 (36.6–84.3)	3.65 (2.38–5.60)
Current smoker (overall)†	323,114	809	276.4 (256.9–295.8)	3.89 (3.46–4.37)	300,996	206	73.6 (63.4–83.8)	4.65 (3.73–5.79)
1–10 cigarettes/day	66,437	131	204.5 (169.4–239.6)	3.11 (2.54–3.80)	94,120	53	58.3 (42.5–74.0)	3.81 (2.76–5.25)
11–20 cigarettes/day	120,202	319	281.9 (250.7–313.1)	4.14 (3.56–4.81)	127,433	88	72.2 (57.0–87.4)	4.78 (3.64–6.27)
21–30 cigarettes/day	75,950	204	295.4 (253.9–336.8)	4.34 (3.66–5.16)	53,174	44	88.6 (62.0–115.2)	5.93 (4.20–8.37)
31–40 cigarettes/day	43,407	113	283.1 (228.6–337.6)	4.33 (3.50–5.35)	20,666	17	98.3 (49.3–147.3)	6.02 (3.62–9.99)
> 40 cigarettes/day	17,118	42	271.5 (185.3–357.7)	4.14 (3.00–5.70)	5,605	4	66.4 (0–132.9)	5.19 (1.92–14.05)

* Adjusted for age, education, ethnicity, and pipe and cigar use.

† Linear trend tests across categories of cigarette smoking were conducted by assigning participants their appropriate category of cigarette smoking and entering this variable as a continuous term in the regression model. P-values were then obtained from the Wald test. All p-values for the test of trend were less than 0.0001.

Table 3

Incidence rates and hazard ratios (95% CIs) for joint categories of smoking dose and cessation

Category	Men				Women				Multivariate adjusted HR*,† for men relative to women (95% CI)
	Person-years	N	Age-standardized incidence rates/10^5 person-years (95% CI)	Multivariate adjusted HR* (95% CI)	Person-years	N	Age-standardized incidence rates/10^5 person-years (95% CI)	Multivariate adjusted HR* (95% CI)	
Overall	2,690,321	3,896	144.0 (139.4–148.5)		1,828,620	627	34.5 (31.8–37.3)		3.71, 3.39–4.06‡
Never smoked cigarettes, pipes, or cigars	677,607	461	69.8 (63.4–76.1)	1.00 (ref)	821,064	133	16.1 (13.4–18.8)	1.00 (ref)	4.07 (3.34–4.97)
Stopped ≥ 10 years ago									
1–10 cigarettes/day	278,413	264	90.6 (79.6–101.6)	1.27 (1.09–1.48)	221,316	62	27.3 (20.5–34.1)	1.70 (1.26–2.30)	3.02 (2.24–4.09)
11–20 cigarettes/day	390,547	557	131.7 (120.7–142.8)	1.79 (1.58–2.04)	142,212	49	33.1 (23.8–42.4)	2.07 (1.49–2.87)	3.81 (2.82–5.14)
21–30 cigarettes/day	249,436	421	159.0 (143.7–174.2)	2.16 (1.88–2.47)	68,696	28	40.7 (25.7–55.8)	2.50 (1.67–3.77)	3.91 (2.65–5.78)
31–40 cigarettes/day	164,686	301	171.6 (152.2–191.1)	2.32 (2.00–2.69)	38,903	16	41.1 (21.0–61.2)	2.54 (1.51–4.26)	4.06 (2.44–6.77)
> 40 cigarettes/day	154,037	307	199.3 (186.7–165.7)	2.52 (2.17–2.92)	28,365	16	56.7 (28.9–84.5)	3.51 (2.09–5.90)	3.33 (2.00–5.55)
Stopped 5–<10 years ago									
1–10 cigarettes/day	22,652	28	128.8 (81.0–176.5)	1.85 (1.26–2.71)	31,866	8	25.8 (7.9–43.7)	1.61 (0.79–3.29)	6.16 (2.69–14.12)
11–20 cigarettes/day	54,351	84	157.4 (123.7–191.0)	2.17 (1.72–2.74)	42,822	22	51.4 (29.9–72.9)	3.21 (2.05–5.05)	3.46 (2.12–5.65)
21–30 cigarettes/day	48,134	106	225.9 (182.8–269.0)	3.09 (2.50–3.82)	25,773	23	92.1 (54.3–130.0)	5.84 (3.75–9.09)	2.09 (1.30–3.36)
31–40 cigarettes/day	38,888	101	271.1 (218.0–324.2)	3.66 (2.95–4.55)	15,764	9	57.8 (19.7–96.0)	3.74 (1.90–7.34)	4.29 (2.14–8.62)
> 40 cigarettes/day	33,302	75	242.9 (187.1–298.7)	3.30 (2.58–4.21)	10,915	7	80.6 (20.5–140.6)	4.45 (2.08–9.52)	3.25 (1.47–7.17)
Stopped 1–5 years ago									
1–10 cigarettes/day	13,080	17	141.8 (73.6–210.0)	2.08 (1.28–3.38)	20,114	10	54.2 (20.5–87.8)	3.32 (1.75–6.32)	1.99 (0.76–5.21)
11–20 cigarettes/day	31,713	68	225.1 (171.5–278.7)	3.08 (2.38–3.98)	29,040	17	61.1 (32.0–90.2)	3.74 (2.26–6.21)	3.86 (2.21–6.74)
21–30 cigarettes/day	27,139	69	278.1 (211.7–344.5)	3.74 (2.90–4.82)	16,412	15	100.8 (49.2–152.5)	6.17 (3.61–10.53)	2.90 (1.62–5.18)
31–40 cigarettes/day	19,354	46	254.3 (180.1–328.5)	3.47 (2.56–4.70)	8,784	4	47.7 (0.9–94.4)	2.90 (1.07–7.86)	6.34 (2.26–17.81)
> 40 cigarettes/day	15,059	39	294.1 (200.1–388.0)	3.89 (2.80–5.40)	4,942	2	51.4 (0–122.6)	2.89 (0.71–11.67)	6.62 (1.58–27.83)
Current smokers									
1–10 cigarettes/day	66,437	131	204.5 (169.4–239.6)	3.11 (2.54–3.80)	94,120	53	58.3 (42.5–74.0)	3.81 (2.76–5.25)	3.81 (2.72–5.33)
11–20 cigarettes/day	120,202	319	281.9 (250.7–313.1)	4.14 (3.56–4.81)	127,433	88	72.2 (57.0–87.4)	4.78 (3.64–6.27)	3.94 (3.09–5.02)
21–30 cigarettes/day	75,950	204	295.4 (253.9–336.8)	4.34 (3.66–5.16)	53,174	44	88.6 (62.0–115.2)	5.93 (4.20–8.37)	3.18 (2.27–4.46)
31–40 cigarettes/day	43,407	113	283.1 (228.6–337.6)	4.33 (3.50–5.35)	20,666	17	98.3 (49.3–147.3)	6.02 (3.62–9.99)	3.14 (1.87–5.29)
> 40 cigarettes/day	17,118	42	271.5 (185.3–357.7)	4.14 (3.00–5.70)	5,605	4	66.4 (0–132.9)	5.19 (1.92–14.05)	3.56 (1.26–10.03)

[*] Adjusted for age, education, ethnicity, and pipe and cigar use.

[†] Risk estimate for male vs. female within specified joint category of cigarette smoking dose and cessation.

[‡] Additionally adjusted for all categories of smoking, pipe, and cigar use.

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Table 4

Relative risks of incident bladder cancer for current smokers relative to never smokers in previously published studies from United States prospective cohorts*

Author, reference, year	Cohort	Sex	Years	Mean age	Never smokers in cohort (N; %)	Cases in never smokers (N; %)	Current smokers in cohort (N; %)	Cases in current smokers (N; %)	Typical amount of cigarettes smoked per day (among current smokers)	RR†† (95%CI) for current smoking
Alberg et al,[44],2007	Washington County MD	Men & women	1963–1978	47[45]	11,722; 26%	20; 22%	20,037; 44%	48; 52%	29% >20 cig/day‡	2.7 (1.6–4.7)
Chyou et al, [46], 1993	Japanese men in Hawaii	Men	1965–1991	54[47]	2,410; 30%	17; 18%	3,495; 44%	60; 63%	77% ≥20 cig/day[48]	2.86 (1.67–4.91)
Mills et al, [49], 1991	Seventh Day Adventists	Men & Women	1976–1982	54[50]	26,059; 76%‡	25; 52%	1,129; 3%‡	4; 8%	32% ≥25 cig/day‡,**	5.67 (1.73–18.61)
Alberg et al, [44], 2007	Washington County MD	Men & women	1975–1994	48[45]	15,249; 32%	40; 23%	17,006; 35%	67; 39%	31% >20 cig/day‡	2.6 (1.7–3.9)
Tripathi et al, [51], 2002	Iowa Women's Health Study	Women	1986–1998	62[52]	24,723; 66%	42; 38%	5,619; 15%	45; 41%	16% >20 cig/day‡,**,[53]	4.23 (2.76–6.70)
Michaud et al, [54], 2001	Health Professionals Follow-up Study	Men	1986–1998	53[55]	24,035; 49%[56]	70; 23%	4,648; 9%	44; 14%	33% > 25 cig/day‡,[55]	2.81 (1.85–4.27)
Cantwell et al, [41], 2006	Breast Cancer Detection Demonstration Project Follow-up Study	Women	1987–2000	55	27,691; 57%‡	62; 44%	7,826; 16%‡	30; 21%	54% >20 cig/day[57]	2.44 (1.56–3.80)
	Summary Estimate†	Men & women				276		298		2.94 (2.45–3.54)

*Not all data on this table was available in the original publication which examined the association of smoking and bladder cancer. For publications which lacked some of these variables, we identified other publications from the same cohort containing the desired information; references for these publications are marked where appropriate.

†Summary relative risk and 95% confidence intervals are from random effect models. The I^2 statistic for heterogeneity across studies was 0.0% and the Cochran Q test p-value for between study heterogeneity was 0.554.

‡Calculated from person-years in the original publication

**Cigarettes smoked per day for both former and current smokers together.

††Alberg and Cantwell used Poisson regression models, Chyou, Mills, and Tripathi used Cox proportional hazards regression, and Michaud used logistic regression.