Association Between Smoking and Risk of Bladder Cancer Among Men and Women

Neal D. Freedman, PhD, MPH
Debra T. Silverman, ScD, ScM
Albert R. Hollenbeck, PhD
Arthur Schatzkin, MD, DrPH†
Christian C. Abnet, PhD, MPH

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

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 National Institutes of Health-AARP (NIH-AARP) Diet and Health Study cohort completed a lifestyle questionnaire and were followed up between October 25, 1995, and December 31, 2006. Previous prospective cohort studies of smoking and incident bladder cancer were identified by systematic review and relative risks were estimated from fixed-effects models with heterogeneity assessed by the I^2 statistic.

Main Outcome Measures Hazard ratios (HRs), PARs, and number needed to harm (NNH).

Results During 4 518 941 person-years of follow-up, incident bladder cancer occurred in 3896 men (144.0 per 100 000 person-years) and 627 women (34.5 per 100 000 person-years). Former smokers (119.8 per 100 000 person-years; HR, 2.22; 95% confidence interval [CI], 2.03-2.44; NNH, 1250) and current smokers (177.3 per 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 per 100 000 person-years). In contrast, the summary risk estimate for current smoking in 7 previous studies (initiated between 1963 and 1987) was 2.94 (95% CI, 2.45-3.54; I^2=0.0%). The PAR 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.

Conclusion Compared with a pooled estimate of US data from cohorts initiated between 1963 and 1987, relative risks for smoking in the more recent NIH-AARP Diet and Health Study cohort were higher, with PARs for women comparable with those for men.

JAMA. 2011;306(7):737-745 www.jama.com

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 Program, incidence rates in white individuals aged 50 years or more have remained stable during the past 30 years (1976-2006), from 123.8 per 100 000 person-years to 142.2 per 100 000 person-years in men and from 32.5 per 100 000 person-years to 33.2 per 100 000 person-years in women; similar patterns are observed in other ethnic and racial groups.[3]

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 during the past 30 years, prevalence of cigarette smoking in the United States has substantially decreased during the same period.[6]

Typically, risk estimates for current smokers have been approximately 3 in previous studies.[5,7] However, the composition of cigarettes has changed during the past 50 years, leading 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, epidemiological studies have observed higher relative risks associated with cigarette smoking for lung cancer.[10] A recent article from the New England Bladder Cancer Study,[11] a large population-based case-control study, suggests that the strength of the cigarette smoking–bladder cancer association may also have increased. In this article, the authors compared the odds ratio (OR) for current smokers relative to never smokers in 3 similar population-based case-control studies performed in New Hampshire in 1994-1998, 1998-2001, and 2001-2004.

Author Affiliations: Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Rockville, Maryland (Drs Freedman, Silverman, Schatzkin, and Abnet); and AARP, Washington, DC (Dr Hollenbeck).
†Died January 20, 2011.
Corresponding Author: Neal D. Freedman, PhD, MPH, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, 6120 Executive Blvd, EPS/320, MSC 7232, Rockville, MD 20852 (freedmanne@mail.nih.gov).

During the course of the 3 studies, the OR associated with current smoking increased from 2.9 (95% confidence interval [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 during the past 30 years. However, these findings need replication, particularly in prospective cohort studies.

Population attributable risks (PARs) for tobacco smoking have been estimated to be 50% to 65% in men and 20% to 30% in women.[5,12-15] However, these estimates were based on studies conducted in populations during periods in which 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 goal 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 National Institutes of Health-AARP (NIH-AARP) Diet and Health Study, initiated October 25, 1995, with follow-up through December 31, 2006.

METHODS

The NIH-AARP Diet and Health Study has been described previously.[18] Briefly, a questionnaire was mailed between 1995 and 1996 to 3.5 million AARP members aged 50 to 71 years who resided in 8 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, and all participants gave written 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 US 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, whichever came first.

Identification of Bladder Cancers

We identified incident bladder cancers by linking the NIH-AARP Diet and Health Study cohort with the cancer registry databases of 10 states (8 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 Diseases for Oncology* (*ICD-O*)[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, and Asian, Pacific Islander, or Native American) was assessed by self-report and was collected 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 methodological 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 6 categories of cigarettes per day (1-10, 11-20, 21-30, 31-40, 41-60, and ≥61); former smokers reported years of smoking cessation using 4 categories (stopped within the last year, stopped 1-4 years ago, stopped 5-9 years ago, and stopped ≥10 years ago). We considered those participants who had quit more than 1 year before baseline as former cigarette smokers. A separate question assessed whether participants had regularly smoked pipes or cigars for 1 year or longer.

Statistical Methods

We completed all NIH-AARP Diet and Health Study analyses using SAS version 9.1 (SAS Institute Inc, Cary, North Carolina), with a 2-sided significance level of $P < .05$. We calculated age-standardized incidence rates and 95% CIs using 5-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 (HRs) and 95% CIs were calculated using Cox proportional hazards regression models.[24] Risk estimates were adjusted for age, education, ethnicity, and pipe or cigar use. Additional adjustment for other possible confounders (alcohol, aspirin and ibuprofen nonsteroidal anti-inflammatory drugs, body mass index [calculated as weight in kilograms divided by height in meters squared], physical activity, self-reported health, intake of fruit, vegetables, or 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 interac-

tion term for follow-up time and cigarette use in the Cox proportional hazards regression models and 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 PARs from multivariate-adjusted β coefficients for ever smoking. The δ method was used to estimate the variance in order to estimate the 95% CIs 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*]) (eFigure, available at http://www.jama.com). 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 then we excluded studies conducted in populations outside of the United States or that lacked data on incident bladder cancer, resulting in 60 studies. We reviewed all 60 published manuscripts, excluding 1 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 vs never smoking. After these exclusions, 6 publications remained that provided data from 7 cohorts. No further publications were identified upon reviewing the references of these 6 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 that lacked 1 or more extraction variables, we sought this data in previous cohort publications. We did not contact study authors. Two coauthors (N.D.F. and C.C.A.) reviewed each publication to ensure that the data extraction was accurate.

We used Stata version 11.0 (StataCorp LP, College Station, Texas) 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% CIs were calculated using fixed-effects models (Mantel-Haenszel method). We examined possible publication bias using both Begg and Mazudmar *P* value for rank correlation[28] and Egger weighted regression method.[29]

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

RESULTS

Participants with cancer (except nonmelanoma skin cancer) at baseline (n = 51 234), proxy respondents (n = 15 760), those participants who died or who were diagnosed with cancer on the first day of follow-up (n = 13), or those participants who failed to provide information about cigarette use (n = 19 329) or cigar and pipe use (n = 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, were more likely to have ever smoked cigarettes, pipes, or cigars, and to have smoked more than 40 cigarettes per day than women. However, a higher proportion of women than men were current smokers. The median age of smoking initiation was 17 years in the subset of the cohort (118 557 men and 72 030 women) who returned a follow-up questionnaire between October 7, 2004, and December 30, 2004 (TABLE 1).

During the course of 4 518 941 person-years of follow-up, 3896 men and 627 women were newly diagnosed with bladder cancer. Overall incidence rates were 144.0 per 100 000 person-years (95% CI, 139.4-148.5) in men and 34.5 per 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 (69.8 per 100 000 person-years in men and 16.1 per 100 000 person-years in women), former and current smokers had increased risk of bladder cancer in both men (former smokers, 154.6 per 100 000 person-years; adjusted HR, 2.14; 95% CI, 1.92-2.37; NNH, 1179; and current smokers, 276.4 per 100 000 person-years; adjusted HR, 3.89; 95% CI, 3.46-4.37; NNH, 484) and women (former smokers, 40.7 per 100 000 person-years; adjusted HR, 2.52; 95% CI, 2.05-3.10; NNH, 4065; and current smokers, 73.6 per 100 000 person-years; adjusted HR, 4.65; 95% CI, 3.73-5.79; NNH, 1739). The combined risk estimates including both sexes were 2.22 (95% CI, 2.03-2.44) for former smokers (119.8 per 100 000 person-years; NNH, 1250; 95% CI, 1171-1343) and 4.06 (95% CI, 3.66-4.50) for current smokers (177.3 per 100 000 person-years; NNH, 727; 95% CI, 671-794) relative to never smokers (39.8 per 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 or more before baseline had lower incidence rates of bladder cancer than those who quit

1 to 4 years or 5 to 9 years before baseline. Nevertheless, relative to never smokers, relative risks remained increased for men and women who quit even 10 years or more before baseline. In never users of cigarettes, pipe and cigar use was also associated with increased risk of bladder cancer in men (HR, 1.29; 95% CI, 1.07-1.56; 92.5 per 100 000 person-years) relative to nonusers (69.8 per 100 000 person-years; NNH, 4405). 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 per 100 000 person-years vs 34.5 per 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. Increased rates persisted in never smokers in which men (69.8 per 100 000 person-years) had 4.07 (95% CI, 3.34-4.97) times the bladder cancer risk of women who never smoked (16.1 per 100 000 person-years).

The PAR for ever smoking in the NIH-AARP Diet and Health Study was similar in men (0.50; 95% CI, 0.45-0.54) and women (0.52; 95% CI, 0.45-0.59).

We then performed a systematic review and meta-analysis of previously published US prospective cohort studies of current cigarette smoking and incident bladder cancer (eFigure). We identified data from the 7 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 .554. We observed no evidence for publication bias by either Egger weighted regression (P=.32) or Begg and Mazumdar rank correlation method (P=.29).

Addition of risk estimates from the NIH-AARP Diet and Health Study to the meta-analysis increased the summary risk estimate to 3.75 (95% CI, 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=.049).

Table 1. Characteristics of the National Institutes of Health-AARP Diet and Health Study Cohort by Sex[a]

Characteristics	No. (%) of Participants	
	Men (n = 281 394)	Women (n = 186 134)
No. of bladder cancers	3896	627
Age at entry into the cohort, median (IQR), y	62.7 (57.8-66.7)	62.3 (57.5-66.4)
Alcohol intake, drinks per d		
0	57 680 (20.6)	54 236 (29.3)
<1	139 843 (49.8)	107 021 (57.7)
1-3	51 900 (18.5)	19 044 (10.3)
>3	31 149 (11.1)	5152 (2.8)
BMI, median (IQR)	26.6 (24.4-29.4)	25.8 (22.9-29.6)
Education		
<High school	16 274 (5.9)	11 403 (6.3)
12 y (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)
Race/ethnicity		
Non-Hispanic white	260 903 (93.7)	166 590 (90.7)
Non-Hispanic black	7605 (2.7)	10 573 (5.8)
Hispanic	5319 (1.9)	3537 (1.9)
Asian, Pacific Islander, or Native American	4777 (1.7)	2941 (1.6)
Consumption, median (IQR), servings per d		
Fruit	1.3 (0.8-2.1)	1.7 (1.0-2.5)
Vegetable	1.9 (1.4-2.5)	2.2 (1.6-3.1)
Total daily energy intake, median (IQR), kcal	1870 (1435-2428)	1461 (1119-1898)
Cigarette smoking status[b]		
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 No. of cigarettes smoked per d (current and former)		
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)	8883 (4.8)
>40	23 792 (8.5)	5222 (2.8)
Age started smoking, median (IQR), y[c]	17 (13-22)	17 (17-22)
Years since quitting smoking (among former smokers)		
Stopped ≥10 y ago	128 542 (45.7)	50 583 (27.2)
Stopped 5-9 y ago	21 224 (7.5)	13 195 (7.1)
Stopped 1-4 y ago	11 669 (4.2)	8308 (4.5)
Ever regularly smoked pipes or cigars (yes)	81 056 (28.8)	802 (0.4)

Abbreviations: BMI, body mass index, calculated as weight in kilograms divided by height in meters squared; IQR, interquartile range.
[a] Data may not add up to total 467 528 persons because of missing data.
[b] See "Methods" section for definitions of cigarette smoking status.
[c] Available for a subset of the cohort, 118 557 men and 72 030 women who returned a follow-up questionnaire in 2004.

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 October 25, 1995, and December 31, 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 estimates observed in New Hampshire case-control data for cases diagnosed in 1998-2001 and 2002-2004 and higher than those for cases diagnosed in 1994-1998. The 1994-1998 cases had an OR of 2.9 (95% CI, 2.0-4.2), whereas the cases diagnosed in 1998-2001 had an OR of 4.2 (95% CI, 2.8-6.3), and the cases diagnosed in 2002-2004 had an OR 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 7 cohorts was 2.94 (95% CI, 2.45-3.54), which is significantly lower than that observed in our study. These observations parallel those previously reported for lung cancer in which 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 cigarette smoking–bladder cancer association as well. Another potential explanation is the increased awareness of bladder cancer risk in smokers, which may prompt earlier diagnostic workup. Alternatively, differences between our study and past studies could have been due to chance, although a recently published meeting abstract from the VITamins And Lifestyle Study (VITAL) also indicated an HR of 4.0 (95% CI, 2.9-5.8) for current smoking vs never smoking for incident bladder cancer.[45]

Although our data suggest that the association of cigarette smoking with bladder cancer has strengthened, inci-

Table 2. Incidence Rates and Adjusted HRs for Cigarette Smoking and Bladder Cancer by Sex

	Men				Women			
Category	Person-Years	No.	Age-Standardized Incidence Rates per 100 000 Person-Years (95% CI)	Multivariate-Adjusted HR (95% CI)[a]	Person-Years	No.	Age-Standardized Incidence Rates per 100 000 Person-Years (95% CI)	Multivariate-Adjusted HR (95% CI)[a]
Never smoked cigarettes, pipes, or cigars	677 607	461	69.8 (63.4-76.1)	1.00 [Reference]	821 064	133	16.1 (13.4-18.8)	1.00 [Reference]
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	NA	NA
Former smoker (overall)[b]	1 540 789	2483	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 y 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 5-9 y 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 1-4 y 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/d	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/d	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/d	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/d	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/d	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)[b]	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/d	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/d	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/d	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/d	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/d	17 118	42	271.5 (185.3-357.7)	4.14 (3.00-5.70)	5605	4	66.4 (0-132.9)	5.19 (1.92-14.05)

Abbreviations: CI, confidence interval; HR, hazard ratio; NA, not applicable.
[a] Adjusted for age, education, ethnicity, and pipe and cigar use.
[b] 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 .0001.

dence rates have stayed largely constant during this same period. However, 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,[11] suggest that the strengthening of the smoking-related relative risks, perhaps due to changing cigarette composition, may have off-

Table 3. Incidence Rates and Adjusted HRs for Joint Categories of Smoking Dose and Cessation by Sex

	Men				Women				
Category	Person-Years	No.	Age-Standardized Incidence Rates per 100 000 Person-Years (95% CI)	Multivariate-Adjusted HR (95% CI)[a]	Person-Years	No.	Age-Standardized Incidence Rates per 100 000 Person-Years (95% CI)	Multivariate-Adjusted HR (95% CI)[a]	Men vs Women, Multivariate-Adjusted HR (95% CI)[a,b]
Overall	2 690 321	3896	144.0 (139.4-148.5)		1 828 620	627	34.5 (31.8-37.3)		3.71 (3.39-4.06)[c]
Never smoked cigarettes, pipes, or cigars	677 607	461	69.8 (63.4-76.1)	1.00 [Reference]	821 064	133	16.1 (13.4-18.8)	1.00 [Reference]	4.07 (3.34-4.97)
Stopped ≥10 y ago									
1-10 cigarettes/d	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/d	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/d	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/d	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/d	154 037	307	186.7 (165.7-207.7)	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 5-9 y ago									
1-10 cigarettes/d	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/d	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/d	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/d	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/d	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 1-4 y ago									
1-10 cigarettes/d	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/d	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/d	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/d	19 354	46	254.3 (180.1-328.5)	3.47 (2.56-4.70)	8784	4	47.7 (0.9-94.4)	2.90 (1.07-7.86)	6.34 (2.26-17.81)
>40 cigarettes/d	15 059	39	294.1 (200.1-388.0)	3.89 (2.80-5.40)	4942	2	51.4 (0-122.6)	2.89 (0.71-11.67)	6.62 (1.58-27.83)
Current smokers									
1-10 cigarettes/d	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/d	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/d	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/d	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/d	17 118	42	271.5 (185.3-357.7)	4.14 (3.00-5.70)	5605	4	66.4 (0-132.9)	5.19 (1.92-14.05)	3.56 (1.26-10.03)

Abbreviations: CI, confidence interval; HR, hazard ratio.
[a] Adjusted for age, education, ethnicity, and pipe and cigar use.
[b] Risk estimates for men vs women within specified joint category of cigarette smoking dose and cessation.
[c] Additionally adjusted for all categories of smoking, pipe, and cigar use.

set the effect of declining smoking prevalence, at least to some extent, contributing to relatively stable incidence rates of bladder cancer during the past 30 years. Future work is needed to investigate this hypothesis.

In the NIH-AARP Diet and Health Study cohort, in which the prevalence of smoking is generally similar in men and women, as observed in the US population,[16,17] the PAR for smoking was approximately 50% in both sexes. Previous studies have found PARs of 50% to 65% in men and 20% to 30% in women,[5,12-15] but were conducted in populations in which the prevalence of smoking in women was considerably lower than in men.[46] 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 article to our knowledge 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.[47] Incidence rates of lung cancer, similar to bladder cancer, are higher in men than in women worldwide.[1] Historically higher rates of tobacco smoking in men relative to women likely explain most of the excess lung cancer cases in men. Because the prevalence of tobacco smoking in women has increased,[48] incidence rates of lung cancer in men and women have converged in many countries, including the United States.[16,48,49] Furthermore, we demonstrated similar incidence rates of lung cancer in men and women of the NIH-AARP Diet and Health Study cohort, both among men and women who smoked similar amounts and among never smokers.[50]

In contrast with the lung, incidence rates of bladder cancer have not converged in men and women,[7] even in countries such as the United States in which men and women now smoke similar amounts.[49] In our study, we ob-

Table 4. Relative Risks of Incident Bladder Cancer for Current Smokers Relative to Never Smokers in Previously Published Studies From US Prospective Cohorts[a]

					No. (%) of Participants				Current Smokers	
Source	Cohort	Sex	Years	Mean Age, y	Never Smokers in Cohort	Cases in Never Smokers	Current Smokers in Cohort	Cases in Current Smokers	Percentage of Current Smokers Who Smoked ≥1 Pack of Cigarettes/d (Actual Cut Point Used in Each Cohort)	RR (95% CI)[b]
Alberg et al,[30] 2007	Washington County, Maryland	Both	1963-1978	47[31]	11 722 (26)	20 (22)	20 037 (44)	48 (52)	29 (>20 cigarettes/d)[c]	2.7 (1.6-4.7)
Chyou et al,[32] 1993	Japanese men in Hawaii	Men	1965-1991	54[33]	2410 (30)	17 (18)	3495 (44)	60 (63)	77 (≥20 cigarettes/d)[34]	2.86 (1.67-4.91)
Mills et al,[35] 1991	Seventh Day Adventists	Both	1976-1982	54[36]	26 059 (76)[c]	25 (52)	1129 (3)[c]	4 (8)	32 (≥25 cigarettes/d)[c,d]	5.67 (1.73-18.61)
Alberg et al,[30] 2007	Washington County, Maryland	Both	1975-1994	48[31]	15 249 (32)	40 (23)	17 006 (35)	67 (39)	31 (>20 cigarettes/d)[c]	2.6 (1.7-3.9)
Tripathi et al,[37] 2002	Iowa Women's Health Study	Women	1986-1998	62[38]	24 723 (66)	42 (38)	5619 (15)	45 (41)	16 (>20 cigarettes/d)[39,c,d]	4.23 (2.76-6.70)
Michaud et al,[40] 2001	Health Professionals Follow-up Study	Men	1986-1998	53[41]	24 035 (49)[42]	70 (23)	4648 (9)	44 (14)	33 (>25 cigarettes/d)[41,c]	2.81 (1.85-4.27)
Cantwell et al,[43] 2006	Breast Cancer Detection Demonstration Project Follow-up Study	Women	1987-2000	55	27 691 (57)[c]	62 (44)	7826 (16)[c]	30 (21)	54 (>20 cigarettes/d)[44]	2.44 (1.56-3.80)
Summary estimate[e]		Both				276		298		2.94 (2.45-3.54)

Abbreviations: CI, confidence interval; RR, relative risk.
[a] Not all data were available in the original publication that examined the association of smoking and bladder cancer. For publications that 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.
[b] Alberg et al[30] and Cantwell et al[43] used Poisson regression models; Chyou et al,[32] Mills et al,[35] and Tripathi et al[37] used Cox proportional hazards regression models; and Michaud et al[40] used logistic regression.
[c] Calculated from person-years in the original publication.
[d] Cigarettes smoked per day for both former and current smokers combined.
[e] Summary RR and 95% CI are from fixed-effects models. The I^2 statistic for heterogeneity across studies was 0.0% and the Cochran Q test P value for between-study heterogeneity was .554.

served 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,[15] a population-based case-control study conducted in 1978. In this study, as in our study, risk of bladder cancer remained higher in men vs women who were never smokers. Although differences in the prevalence of smoking are likely an important explanation for the excess of bladder cancer in men in many parts of the world where cigarette smoking is substantially more common in men than in women,[51,52] 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, because men in general are more likely than women to work in specific occupations that have been traditionally associated with bladder cancer risk (ie, aromatic amine-manufacturing workers, leather workers, painters, truck drivers, machinists, and aluminum workers).[5,53-55] We lacked assessment of occupation in our study; however, bladder cancer risk among men in the National Bladder Cancer Study was attenuated after adjustment for occupational exposures, but remained increased relative to women.[15] Alternatively, physiological 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,[43,56,57] 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. However, several limitations should be noted. We lacked information about the age at smoking initiation for a majority of cohort participants and so could not calculate smoking duration or pack-years. Among the subset of cohort participants (118 557 men and 72 030 women) returning a follow-up questionnaire between October 7, 2004, and December 30, 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 during the course of follow-up. Because a number of participants probably quit during follow-up, risk estimates for current smoking in our study are likely to be attenuated. In addition, our results may not apply to other populations, particularly those in other countries that may differ in smoking prevalence and cigarette composition.

In conclusion, 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 Diet and Health Study 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.

Author Contributions: Dr Freedman had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Freedman, Silverman, Hollenbeck, Schatzkin, Abnet.
Acquisition of data: Hollenbeck, Schatzkin.
Analysis and interpretation of data: Freedman, Silverman, Abnet.
Drafting of the manuscript: Freedman, Silverman, Abnet.
Critical revision of the manuscript for important intellectual content: Freedman, Silverman, Hollenbeck, Schatzkin, Abnet.
Statistical analysis: Freedman, Silverman, Abnet.
Obtained funding: Schatzkin.
Study supervision: Freedman, Hollenbeck, Schatzkin, Abnet.
Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.
Funding/Support: This research was supported by the Intramural Research Program of the National Institutes of Health, National Cancer Institute, Division of Cancer Epidemiology and Genetics. Cancer incidence data from Arizona were 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 Florida 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; and from Texas by the Texas Cancer Registry.
Role of the Sponsor: The sponsor reviewed and approved final submission but had no role in the design and conduct of the study; in the collection, analysis, and interpretation of the data; or in the preparation of the manuscript.
Disclaimer: 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.
Online-Only Material: An eFigure is available at http://www.jama.com.
Additional Information: This article is dedicated to the memory of Arthur Schatzkin, MD, DrPH.
Additional Contributions: We thank the participants of the NIH-AARP Diet and Health Study for their outstanding cooperation.

REFERENCES

1. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. *CA Cancer J Clin*. 2005;55(2):74-108.
2. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. *CA Cancer J Clin*. 2010;60(5):277-300.
3. Fast Stats. An interactive tool for access to SEER cancer statistics. Surveillance Research Program, National Cancer Institute. http://seer.cancer.gov/faststats. Accessed July 11, 2011.
4. Tobacco Smoke and Involuntary Smoking. In: *IARC Monographs on the Evaluation of Carcinogenic Risk to Humans*. Vol 83. Lyon, France: IARC; 2004.
5. Silverman DT, Devesa SS, Moore LE, Rothman N. Bladder cancer. In: Schottenfeld D, Fraumeni JF Jr, eds. *Cancer Epidemiology and Prevention*. 3rd ed. New York, NY: Oxford University Press; 2006:1101-1127.
6. Garrett BE, Dube SR, Trosclair A, Caraballo RS, Pechacek TF; Centers for Disease Control and Prevention (CDC). Cigarette smoking—United States, 1965-2008. *MMWR Surveill Summ*. 2011;60(suppl):109-113.
7. Hemelt M, Yamamoto H, Cheng KK, Zeegers MP. The effect of smoking on the male excess of bladder cancer: a meta-analysis and geographical analyses. *Int J Cancer*. 2009;124(2):412-419.
8. Wynder EL, Hoffmann D. Smoking and lung cancer: scientific challenges and opportunities. *Cancer Res*. 1994;54(20):5284-5295.
9. Hoffmann D, Hoffmann I, El-Bayoumy K. The less harmful cigarette: a controversial issue: a tribute to Ernst L. Wynder. *Chem Res Toxicol*. 2001;14(7):767-790.
10. Thun MJ, Lally CA, Flannery JT, Calle EE, Flanders WD, Heath CW Jr. Cigarette smoking and changes in the histopathology of lung cancer. *J Natl Cancer Inst*. 1997;89(21):1580-1586.
11. Baris D, Karagas MR, Verrill C, et al. A case-control study of smoking and bladder cancer risk: emer-

gent patterns over time. *J Natl Cancer Inst*. 2009; 101(22):1553-1561.
12. Brennan P, Bogillot O, Cordier S, et al. Cigarette smoking and bladder cancer in men: a pooled analysis of 11 case-control studies. *Int J Cancer*. 2000; 86(2):289-294.
13. D'Avanzo B, La Vecchia C, Negri E, Decarli A, Benichou J. Attributable risks for bladder cancer in northern Italy. *Ann Epidemiol*. 1995;5(6):427-431.
14. Hartge P, Silverman D, Hoover R, et al. Changing cigarette habits and bladder cancer risk: a case-control study. *J Natl Cancer Inst*. 1987;78(6):1119-1125.
15. Hartge P, Harvey EB, Linehan WM, et al. Unexplained excess risk of bladder cancer in men. *J Natl Cancer Inst*. 1990;82(20):1636-1640.
16. Devesa SS, Bray F, Vizcaino AP, Parkin DM. International lung cancer trends by histologic type: male:female differences diminishing and adenocarcinoma rates rising. *Int J Cancer*. 2005;117(2):294-299.
17. Centers for Disease Control and Prevention (CDC). Vital signs: current cigarette smoking among adults aged >or=18 years—United States, 2009. *MMWR Morb Mortal Wkly Rep*. 2010;59(35): 1135-1140.
18. Schatzkin A, Subar AF, Thompson FE, et al. Design and serendipity in establishing a large cohort with wide dietary intake distributions: the National Institutes of Health-American Association of Retired Persons Diet and Health Study. *Am J Epidemiol*. 2001; 154(12):1119-1125.
19. Michaud DS, Midthune D, Hermansen S, et al. Comparison of cancer registry case ascertainment with SEER estimates and self-reporting in a subset of the NIH-AARP Diet and Health Study. *J Registry Manag*. 2005;32(2):70-75.
20. Fritz AG. *International Classification of Diseases for Oncology, ICD-O*. 3rd ed. Geneva, Switzerland: World Health Organization; 2000.
21. Assaf AR, Parker D, Lapane KL, McKenney JL, Carleton RA. Are there gender differences in self-reported smoking practices? correlation with thiocyanate and cotinine levels in smokers and nonsmokers from the Pawtucket Heart Health Program. *J Womens Health (Larchmt)*. 2002;11(10):899-906.
22. Petitti DB, Friedman GD, Kahn W. Accuracy of information on smoking habits provided on self-administered research questionnaires. *Am J Public Health*. 1981;71(3):308-311.
23. Breslow NE, Day NE. *Statistical Methods in Cancer Research. Vol II: The Design and Analysis of Cohort Studies*. Lyon, France: International Agency for Research on Cancer; 1987.
24. Cox DR. Regression models and life-tables. *J R Stat Soc Series B Stat Methodol*. 1972;34(2):187-220.
25. Bruzzi P, Green SB, Byar DP, Brinton LA, Schairer C. Estimating the population attributable risk for multiple risk factors using case-control data. *Am J Epidemiol*. 1985;122(5):904-914.
26. Spiegelman D, Hertzmark E, Wand HC. Point and interval estimates of partial population attributable risks in cohort studies: examples and software. *Cancer Causes Control*. 2007;18(5):571-579.
27. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003; 327(7414):557-560.
28. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics*. 1994;50(4):1088-1101.
29. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315(7109):629-634.
30. Alberg AJ, Kouzis A, Genkinger JM, et al. A prospective cohort study of bladder cancer risk in relation to active cigarette smoking and household exposure to secondhand cigarette smoke. *Am J Epidemiol*. 2007;165(6):660-666.
31. Gallicchio L, Kouzis A, Genkinger JM, et al. Active cigarette smoking, household passive smoke exposure, and the risk of developing pancreatic cancer. *Prev Med*. 2006;42(3):200-205.
32. Chyou PH, Nomura AM, Stemmermann GN. A prospective study of diet, smoking, and lower urinary tract cancer. *Ann Epidemiol*. 1993;3(3):211-216.
33. Rodriguez BL, D'Agostino R, Abbott RD, et al. Risk of hospitalized stroke in men enrolled in the Honolulu Heart Program and the Framingham Study: a comparison of incidence and risk factor effects. *Stroke*. 2002;33(1):230-236.
34. Rodriguez BL, Sharp DS, Abbott RD, et al. Fish intake may limit the increase in risk of coronary heart disease morbidity and mortality among heavy smokers: the Honolulu Heart Program. *Circulation*. 1996; 94(5):952-956.
35. Mills PK, Beeson WL, Phillips RL, Fraser GE. Bladder cancer in a low risk population: results from the Adventist Health Study. *Am J Epidemiol*. 1991; 133(3):230-239.
36. Butler TL, Fraser GE, Beeson WL, et al. Cohort profile: the Adventist Health Study-2 (AHS-2). *Int J Epidemiol*. 2008;37(2):260-265.
37. Tripathi A, Folsom AR, Anderson KE; Iowa Women's Health Study. Risk factors for urinary bladder carcinoma in postmenopausal women. *Cancer*. 2002; 95(11):2316-2323.
38. Munger RG, Folsom AR, Kushi LH, Kaye SA, Sellers TA. Dietary assessment of older Iowa women with a food frequency questionnaire: nutrient intake, reproducibility, and comparison with 24-hour dietary recall interviews. *Am J Epidemiol*. 1992;136(2):192-200.
39. Limsui D, Vierkant RA, Tillmans LS, et al. Cigarette smoking and colorectal cancer risk by molecularly defined subtypes. *J Natl Cancer Inst*. 2010; 102(14):1012-1022.
40. Michaud DS, Clinton SK, Rimm EB, Willett WC, Giovannucci E. Risk of bladder cancer by geographic region in a U.S. cohort of male health professionals. *Epidemiology*. 2001;12(6):719-726.
41. Rimm EB, Chan J, Stampfer MJ, Colditz GA, Willett WC. Prospective study of cigarette smoking, alcohol use, and the risk of diabetes in men. *BMJ*. 1995; 310(6979):555-559.
42. Fuchs CS, Colditz GA, Stampfer MJ, et al. A prospective study of cigarette smoking and the risk of pancreatic cancer. *Arch Intern Med*. 1996;156(19): 2255-2260.
43. Cantwell MM, Lacey JV Jr, Schairer C, Schatzkin A, Michaud DS. Reproductive factors, exogenous hormone use and bladder cancer risk in a prospective study. *Int J Cancer*. 2006;119(10):2398-2401.
44. Moore SC, Mayne ST, Graubard BI, et al. Past body mass index and risk of mortality among women. *Int J Obes (Lond)*. 2008;32(5):730-739.
45. Hotaling J, Wright J, Porter M, White E. Smoking and risk of urothelial cell carcinoma of the bladder: results from a contemporary, prospective cohort study. *J Urol*. 2010;183(4):e449.
46. Puente D, Hartge P, Greiser E, et al. A pooled analysis of bladder cancer case-control studies evaluating smoking in men and women. *Cancer Causes Control*. 2006;17(1):71-79.
47. US Department of Health and Human Services. *The Health Consequences of Smoking: A Report of the Surgeon General*. Atlanta, GA: US Dept of Health and Human Services, Centers for Disease Control and Prevention; 2004.
48. Jemal A, Travis WD, Tarone RE, Travis L, Devesa SS. Lung cancer rates convergence in young men and women in the United States: analysis by birth cohort and histologic type. *Int J Cancer*. 2003;105(1): 101-107.
49. Cook MB, Dawsey SM, Freedman ND, et al. Sex disparities in cancer incidence by period and age. *Cancer Epidemiol Biomarkers Prev*. 2009;18(4):1174-1182.
50. Freedman ND, Leitzmann MF, Hollenbeck AR, Schatzkin A, Abnet CC. Cigarette smoking and subsequent risk of lung cancer in men and women: analysis of a prospective cohort study. *Lancet Oncol*. 2008; 9(7):649-656.
51. Warner KE. The role of research in international tobacco control. *Am J Public Health*. 2005;95(6): 976-984.
52. Samanic C, Kogevinas M, Dosemeci M, et al. Smoking and bladder cancer in Spain: effects of tobacco type, timing, environmental tobacco smoke, and gender. *Cancer Epidemiol Biomarkers Prev*. 2006; 15(7):1348-1354.
53. Colt JS, Baris D, Stewart P, et al. Occupation and bladder cancer risk in a population-based case-control study in New Hampshire. *Cancer Causes Control*. 2004;15(8):759-769.
54. Dryson E, 't Mannetje A, Walls C, et al. Case-control study of high risk occupations for bladder cancer in New Zealand. *Int J Cancer*. 2008;122(6): 1340-1346.
55. Samanic CM, Kogevinas M, Silverman DT, et al. Occupation and bladder cancer in a hospital-based case-control study in Spain. *Occup Environ Med*. 2008; 65(5):347-353.
56. Davis-Dao CA, Henderson KD, Sullivan-Halley J, et al. Lower risk in parous women suggests that hormonal factors are important in bladder cancer etiology. *Cancer Epidemiol Biomarkers Prev*. 2011;20(6): 1156-1170.
57. McGrath M, Michaud DS, De Vivo I. Hormonal and reproductive factors and the risk of bladder cancer in women. *Am J Epidemiol*. 2006;163(3):236-244.