Research Article

Cancer Prevention Research

Smoking Cessation and the Risk of Bladder Cancer among Postmenopausal Women

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Abstract

Smoking is the strongest established risk factor for bladder cancer. Former smokers have a lower risk of bladder cancer compared with current smokers, but findings on the dose–response relationship between years after quitting and the risk of bladder cancer are inconsistent. A total of 143,279 postmenopausal women from the Women's Health Initiative Study were included. Cox proportional hazards regression models were applied for estimating age- and multivariable-adjusted HRs and their 95% confidence intervals (CI). There were 870 bladder cancer cases identified over an average of 14.8 years of follow-up. After adjusting for pack-years of smoking, bladder cancer risk among former smokers declined by 25% within the first 10 years of cessation and continued to decrease as cessation time increased but remained higher than never smokers after 30 years of quitting (HR, 1.92; 95% CI, 1.43–2.58). Smokers who quit smoking had a lower risk of bladder cancer compared with current smokers (HR, 0.61; 95% CI, 0.40–0.94). We conclude that among postmenopausal women, there is a significant reduction in the risk of bladder cancer after quitting smoking. In addition to primary prevention, smoking cessation is critical to prevent the incidence of bladder cancer in older women.

Introduction

Bladder cancer is the ninth most common cancer worldwide, with incidence rates especially higher in Europe and North America compared with Asia (1, 2). Epidemiologic evidence indicates that bladder cancer is more common among males, older adults, and white populations due to genetic susceptibilities (3, 4). In the United States, bladder cancer ranks as the fourth most common cancer in men and ninth most common cancer in women (5). Previous findings suggested that postmenopausal women may have a higher risk of bladder cancer compared with women who had not undergone menopause, although the possible reasons are still under investigation (6). In addition, women with bladder cancer often have more serious prognoses and tend to have worse outcomes in comparison with men even when bladder cancers are at similar stages (7). Most of previous studies regarding risk factors for bladder cancer have been focused on men or the general population (8, 9), and studies conducted among older women are insufficient.

Smoking has been recognized as the strongest established risk factor for bladder cancer, accounting for approximately 65% of disease risk in men and 20% to 30% in women (10, 11). The chemicals contained in cigarettes, such as 2-naphthylamine, 4-aminobiphenyl and other arylamines, are known as bladder carcinogens (12–14). Other well-established and potential risk factors for both genders include occupational exposure to dyestuffs, low fruit and vegetable intake, obesity, and family history (9). In female nonsmokers, environmental exposure to secondhand smoking is also suggested to be related to higher risk of bladder cancer (14, 15).

Epidemiologic studies have found that the strength of the smoking–bladder cancer association rises with increases in smoking intensity (cigarettes per day) and duration (16). Former smokers have a significantly lower risk of bladder cancer in comparison with current smokers (10, 17, 18), but findings on the dose–response relationship between cessation time and risk of bladder cancer are inconsistent. It is also unclear whether the risk of bladder cancer among former smokers ever normalizes to that of never smokers after quitting smoking (9, 16, 19–22). However, most of these studies were case–control studies, and none of them were among postmenopausal women. Because the proportion of former smokers

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continues to increase, and the number of former smokers has exceeded that of current smokers since 2005 (23), conducting a prospective cohort study among postmenopausal women—a population with a large proportion of former smokers—will help to clarify these previous findings (22, 24).

It is also suggested that the molecular pathways regarding muscle-invasive bladder cancer and non–muscle-invasive bladder carcinoma *in situ* are different. However, it is not clear that whether the smoking cessation is related to similar risks reduction of the different subtypes of bladder cancer (25–31). In this study, we investigated the dose–response relationship between years since quitting (YSQ) smoking and the risk of bladder cancer among postmenopausal women who were former smokers, and further explored if these associations differed between two subtypes of bladder cancer—transitional and papillary bladder cancer.

Materials and Methods

Study population

The Women's Health Initiative (WHI) Study was established to investigate major causes of morbidity and mortality among postmenopausal women (32). Detailed information about design, scientific rationale, eligibility, and baseline characteristics of the participants and recruitment methods of WHI has been published elsewhere (33, 34). In this study, we used data from WHI clinical trials and observational study. A total of 161,808 postmenopausal women ages 50 to 79 years were recruited between 1993 and 1998 and were followed up every 6 to 12 months. Participated women were asked to complete self-report screening and enrolment questionnaires, interviews, physical examinations, and blood sample collection. Written-informed consent and appropriate Institutional Review Board approval were obtained by each participating WHI site. Because women with prevalent cancers were more likely to be advised to adopt healthy lifestyles (including quitting smoking) by their healthcare providers, we excluded women with cancer other than melanoma skin cancer at baseline (n = 12,655). Women whose information on smoking was missing at baseline (n = 1,959) were also excluded. The primary exposure in our study was smoking cessation, so in the primary analysis, we also excluded former smokers whose information on age of quitting smoking was missing (n = 3,915), reaching 143,279 postmenopausal women for primary data analysis.

Exposure assessment

In the WHI, information about smoking was collected at baseline and during the follow-ups. The participated women were asked "during your entire life, have you smoked at least 100 cigarettes" at the entry of the study. Participants who answered no were categorized as never smoked, and those who answered yes were categorized as ever smokers. Ever smokers were then grouped into former or current smokers based on their answer to the question "Do you smoke cigarettes now?" A new variable representing YSQ for each former smoker was calculated as the difference between age at baseline and median age of quitting smoking, and then categorized into <10, 10–<20, 20–<30, and ≥30 years or more. Updated information on smoking was collected in the clinical trials and observational study at years 1, 3, 4, 5, 6, 7, and 8, by asking "Do you smoke cigarettes now?" For baseline current smokers, those who answered "no" to this question during follow-ups were categorized as new quitters, and those who answered "yes" were categorized as current smokers during follow-ups. For baseline former smokers, the total nonsmoking years during follow-ups were added to their total YSQ. For those who quit smoking and then relapsed during the follow-ups, the total years since quitting smoking was computed as the total years they stayed away from smoking. Women whose information on smoking during follow-ups was missing, their answers to smoking status during their last available visits were used.

Number of cigarettes per day was collected by answers to the question "on the average, how many cigarettes do you (did you) usually smoke each day?" The variable was originally categorized as "<1," "1—4," "5–14," "15–24," "25–34," "35–44," and "≥45." Based on the data distribution and previous study (35), we recategorized the variable as "<5," "5–<15," "15–<25," and "≥25" cigarettes per day. Pack-years of smoking was computed from total years of smoking and numbers of cigarettes per day.

Outcome assessment

In the WHI, bladder cancer incidence was documented and coded for primary site. The diagnosis of bladder cancer was initially identified through self-administered questionnaires, then confirmed by a centralized review of medical records, including pathology reports (if the resections or biopsies were available) from diagnostic aspirations, surgeries, and discharge summaries, and subsequently adjudicated by trained, central adjudicators.

The histology subtypes of bladder cancer sites were coded according to the ICD-O-2 (International Classification of Diseases for Oncology, Second Edition). In this study, we excluded carcinoma *in situ*. Based on the National Cancer Institute (NIH) bladder cancer morphology and grade description, we described bladder cancer as three subtypes: transitional cell carcinoma, papillary carcinoma, and other types (including squamous cell carcinoma, adenocarcinoma, small cell carcinoma, lymphoepithelial carcinoma, hemangiosarcoma, clear cell adenocarcinoma, and undifferentiated carcinoma; ref. 36).

Statistical analysis

Baseline characteristics were examined by participants' smoking status. ANOVA was performed to test the difference for continuous variables, and χ^2 tests were used to test

for categorical variables, across different groups of smoking status.

Potential confounders were determined based on previous studies and by covariates whose parameter estimates changed more than 10% after being added to the model. Confounders that were used in multivariable analysis included age at enrollment (in continuous), race/ethnicity (American Indian or Alaskan Native, Asian or Pacific Islander, Black or African-American, Hispanic/Latino, White not of Hispanic origin, and others), education (high school or less, some college or technical training, college or post-college, and master's degree or higher), occupation (homemaker/raising children/other, managerial/professional specialty, technical/sales/administrative support, service, operator/fabricator/laborers, and others), marital status (never married, divorced or separated, widowed, presently married, and marriage-like relationship such as living together for $\geq$2 years or living together <2 years but have children together), alcohol intake (nondrinker, former drinker, and current drinker), physical activity (no activity, some activity or limited duration, 2–<4 episodes per week, and $\geq$4 episodes per week), family cancer history (yes/no), body mass index (BMI, <25, 25–29.9, and $\geq$30 kg/m^2), daily dietary energy intake (kcal, in continuous) and percentage of calories from fat (%, in continuous), and daily fruit and vegetable consumption (medium portion of servings, in continuous).

Cox proportional hazard regression models were used to estimate age-adjusted and multivariable-adjusted HRs and 95% confidence intervals (CI). We performed four sequential models to analyze the association between YSQ and the risk of bladder cancer (4, 9, 37): Model 1 was adjusted for age only. Model 2 was additionally adjusted for education, race/ethnicity, occupation, marital status, alcohol consumption, physical activity, family history of cancer, BMI, daily total energy intake and percentage of energy from fat, and daily fruit and vegetable consumption. Model 3 was adjusted for variables that were adjusted in Model 2 and cigarettes per day. Model 4 was adjusted for the variables that were adjusted in Model 2 and pack-years of smoking. Trend test was performed among former smokers to examine the linear dose–response relationship between YSQ and risk of bladder cancer by treating the median values of each YSQ category as continuous variable in the multivariable-adjusted Cox proportional hazard regression models.

Follow-up time for each participant was calculated as the time between the date of enrollment and the date of bladder cancer diagnosis, loss-to-follow-up, death, or administrative censoring date, whichever came first. When using data incorporated with follow-up information, there were less than 1,000 women who had quit smoking for fewer than 10 years, so we combined YSQ less than 10 and 10–20 years into one category as YSQ less than 20 years. We then performed two separate analyses to examine the association between YSQ and risk of bladder cancer using smoking status from both baseline and follow-ups. We first examined the association by treating women who quit smoking during follow-ups as a separate group. In the second method, women who quit smoking during follow-ups were treated as former smokers, and their total nonsmoking years were combined with YSQ of baseline former smokers to calculate the new YSQ. Model 4 from the primary analysis was reconducted by treating women who continued to smoke during follow-ups as the reference group.

We assessed the relation between smoking cessation and subtypes of bladder cancer risks using a joint Cox model, in which transitional and papillary bladder cancer were modeled at the same time, adjusted for covariates from Model 4 in the primary analysis (38).

Finally, to compare the difference in risk of bladder cancer between women who continued smoking and those who quit during follow-up, we performed a secondary analysis using time-updated smoking status.

All statistical analyses were conducted using SAS (Version 9.4, SAS Institute). Two-sided P values were reported, and a $P \leq 0.05$ was considered statistically significant.

Results

By February 28, 2017, 870 bladder cancer cases occurred. Among the postmenopausal women included in the study, there were 75,458 (52.67%) never smokers, 57,606 (40.21%) former smokers, and 10,215 (7.13%) current smokers. The baseline characteristics of the participants by smoking status are shown in Table 1. In comparison to never smokers, former smokers were slightly younger, more likely to be non-Hispanic White, tend to have lower BMI, to hold higher degrees, to work in managerial or professional fields, to be divorced or separated, to have a higher rate of family history of cancers, to be current drinkers, and to have low fat dietary intake.

The association between YSQ and bladder cancer risk is shown in Table 2. When adjusting for age only, in comparison with never smokers, former smokers and current smokers had 2.01 (95% CI, 1.74–2.33) and 3.39 (95% CI, 2.71–4.24) times the risk of bladder cancer, respectively. After further adjusting for race/ethnicity, education level, occupation, marital status, alcohol consumption, BMI, family history of cancer, physical activity, and daily food consumption, the results from Model 2 (Table 2) showed that bladder cancer continued to decrease with greater YSQ (P for trend: <0.0001), with HR = 2.77 (95% CI, 2.17–3.53) for YSQ < 10 years, HR = 2.19 (95% CI, 1.75–2.74) for YSQ 10–<20 years, and HR = 1.96 (95% CI, 1.55–2.47) for YSQ 20–<30 years. For former smokers who quit smoking for 30 years or longer, there was no significant difference in risk of bladder cancer between former and never smokers (HR, 1.28; 95% CI, 0.99–1.65). However,

Table 1. Baseline characteristics of the study participants by smoking status in the WHI study

Variable[a]	Never smokers	Former smokers	Current smokers	*P* value[b]
Total sample [*n* (%)]	75,458 (52.4)	57,606 (40.2)	10,215 (7.1)	<0.0001
Baseline age (mean ± SD, years)	63.53 ± 7.3	63.09 ± 7.1	61.07 ± 6.8	<0.0001
Race/ethnicity (%)				<0.0001
American Indian/Alaska	336 (0.4)	251 (0.4)	68 (0.6)	
Asian/Pacific Islander	2,955 (3.7)	940 (1.5)	165 (1.5)	
Black/African-American	6,881 (8.7)	4,953 (8.1)	1,590 (14.6)	
Hispanic/Latino	3,904 (4.9)	1,664 (2.7)	451 (4.1)	
Non-Hispanic White	64,395 (81.1)	52,781 (86.2)	8,507 (78.0)	
Other	981 (1.2)	618 (1.0)	133 (1.2)	
Education level (%)				<0.0001
High school/less	19,033 (24.1)	12,232 (20.1)	2,881 (26.5)	
Some college/tech training	28,665 (36.3)	23,802 (39.1)	4,725 (43.5)	
College/some post-college	17,359 (22.0)	14,307 (23.5)	1,983 (18.3)	
Master/higher	13,974 (17.7)	10,544 (17.3)	1,278 (11.8)	
Occupation (%)				<0.0001
Managerial/professional	29,946 (37.7)	24,864 (40.6)	3,701 (33.9)	
Technical/sales	21,552 (27.1)	16,877 (27.6)	3,219 (29.5)	
Service/labor	13,189 (16.6)	9,452 (15.4)	2,192 (20.1)	
Homemaker only	8,391 (10.6)	5,316 (8.7)	835 (7.7)	
Marital status (%)				<0.0001
Never married	3,549 (4.5)	2,505 (4.1)	591 (5.4)	
Divorced/separated	10,551 (13.3)	10,686 (17.5)	2,897 (26.5)	
Widowed	13,680 (17.2)	10,299 (16.8)	2,080 (19.1)	
Presently married	50,625 (63.7)	35,672 (59.8)	5,076 (46.5)	
Marriage-like relationship	1,047 (1.3)	1,145 (1.9)	270 (2.5)	
BMI (%, kg/m^2)				<0.0001
<25	27,874 (35.1)	20,450 (33.4)	4,410 (40.4)	
25–<30	27,201 (34.2)	21,188 (34.6)	3,712 (34.0)	
≥30	23,719 (29.9)	19,015 (31.1)	2,692 (24.7)	
Physical activity (%)				<0.0001
No activity	11,977 (15.1)	8,523 (13.9)	2,518 (23.1)	
Some activity of limited duration	31,819 (40.1)	22,184 (36.2)	4,812 (44.1)	
2–<4 episodes per week	13,347 (16.8)	10,899 (17.9)	1,402 (12.9)	
≥4 episodes per week	18,762 (23.6)	16,842 (27.5)	1,626 (14.9)	
Alcohol consumption (%)				<0.0001
None drinker	14,735 (18.6)	1,776 (2.9)	396 (3.6)	
Former drinker	13,583 (17.1)	12,373 (20.2)	2,225 (20.4)	
Current drinker	51,134 (64.4)	47,058 (76.9)	8,293 (76.0)	
Family history of cancer (%)				<0.0001
No	26,049 (33.8)	19,011 (32.0)	3,707 (35.3)	
Yes	50,045 (65.0)	39,698 (66.9)	6,633 (63.1)	
Dietary energy (mean ± SD, kcal)	1620.6 ± 724.3	1639.5 ± 691.8	1624.7 ± 785.0	<0.0001
Percent calories from fat (mean ± SD, %)	32.6 ± 8.2	32.3 ± 8.5	35.9 ± 8.4	<0.0001
Daily fruit and vegetable intake (median portion of servings, SD)	4.1 (2.2)	4.1 (2.1)	3.1 (1.9)	<0.0001

[a]Values are *n* (%), if not specified.
[b]*P* values were computed for comparison among never, former, and current smokers.

after further adjusted for numbers of cigarettes per day or pack years of smoking (Models 3 and 4; Table 2, columns 4–5), former smokers with YSQ ≥ 30 still had significantly higher risk of bladder cancer when compared with never smokers (HR, 1.88; 95% CI, 1.37–2.58 and HR, 1.92; 95% CI, 1.43–2.58, respectively).

A total of 1,358 baseline smokers quit smoking during the follow-ups. When only using baseline smoking status (Table 3, column 2), in comparison with current smokers, the most rapid decline in risk of bladder cancer occurred during the first 10 years of smoking cessation (declined rate = 25%). In comparison with those who continued to smoke, women who quit smoking during follow-ups had 39% reduction in bladder cancer risk (HR, 0.61; 95% CI, 0.40–0.94; Table 3). The risk of bladder cancer continued to decline as YSQ increased.

The results from the analysis of the association between smoking cessation and subtypes of bladder cancer followed similar patterns (Table 4). Former smokers who quit smoking for ≥30 years still had elevated risk of bladder cancer of both major subtypes of bladder cancer. In the model that additionally adjusted for pack-years of smoking, former smokers who quit smoking for 30 years or more had 1.88 (95% CI, 0.94–3.76) hazard of transitional bladder cancer and 1.87 (95% CI, 1.31–2.67) hazard of papillary bladder cancer in comparison with never smokers. Results were similar to the model adjusted for cigarettes per day. The HRs for transitional and papillary bladder cancer were similar for both former and current smokers, in comparison with never smokers. The *P* value for the test of difference in HRs across the two subtypes was 0.48 for model adjusted for

Table 2. Age-adjusted and multivariable-adjusted HR of bladder cancer in relation to years since quitting smoking

Variable	Number of cases	Age-adjusted HR (95% CI)	Multivariable-adjusted HR (95% CI)[a]	Multivariable-adjusted HR (95% CI)[b]	Multivariable-adjusted HR (95% CI)[c]
Never smoker (ref)	308	1.00	1.00	1.00	1.00
Former smoker (years since quitting smoking)	458	2.01 (1.74–2.33)	1.96 (1.68–2.28)	2.77 (2.22–3.45)	2.57 (2.18–3.03)
<10	104	2.81 (2.24–3.51)	2.77 (2.17–3.53)	3.25 (2.46–4.28)	2.94 (2.32–3.72)
10–<20	139	2.34 (1.92–2.87)	2.19 (1.75–2.74)	2.84 (2.20–3.45)	2.61 (2.11–3.23)
20–<30	119	2.06 (1.67–2.55)	1.96 (1.55–2.47)	2.61 (1.98–3.45)	2.48 (1.96–3.14)
≥30	91	1.29 (1.02–1.63)	1.28 (0.99–1.65)	1.88 (1.37–2.58)	1.92 (1.43–2.58)
P value for linear trend[d]		<0.0001	<0.0001	<0.0001	<0.0001
Current smoker	104	3.39 (2.71–4.24)	3.24 (2.55–4.11)	4.53 (3.38–6.08)	3.67 (2.87–4.68)

[a]Model 1: adjusted for age, education, race/ethnicity, occupation, marital status alcohol consumption, physical activity, family history of cancer, BMI, daily total energy intake and percentage of energy from fat, daily fruit consumption, and daily vegetable consumption.
[b]Model 2: adjusted for covariates in Model 1+ cigarettes per day.
[c]Model 3: adjusted for covariates in Model 1+ pack-years of smoking.
[d]Trend test was performed among former smokers by treating the median values of each YSQ category as continuous variable in the multivariable-adjusted Cox proportional hazard regression models.

Table 3. Multivariate-adjusted HR of bladder cancer by years since quitting smoking in former smokers compared with current smokers[a]

Variable	Multi-adjusted HR (95% CI)[b]	Variable	Multi-adjusted HR (95% CI)[c]	Multi-adjusted HR (95% CI)[d]
Current smoker	1.00	**Baseline current smoker**		
Current smokers		Continuing smokers during follow-ups	1.00	1.00
New quitters		New quitters	0.61 (0.40–0.94)	
Never smokers	0.23 (0.17–0.31)	**Never smokers**	0.21 (0.17–0.25)	0.19 (0.15–0.24)
Former smoker (years since quitting smoking)	0.61 (0.49–0.77)	**Former smoker (years since quitting smoking)**		
<10	0.75 (0.56–0.99)	—	—	—
10–<20	0.65 (0.50–0.86)	<20	0.55 (0.45–0.66)	0.63 (0.45–0.88)
20–<30	0.60 (0.45–0.79)	20–<30	0.48 (0.33–0.68)	0.58 (0.49–0.69)
≥30	0.43 (0.32–0.59)	≥30	0.39 (0.27–0.55)	0.39 (0.28–0.55)
P value for linear trend[e]	<0.0001	***P* value for linear trend**[¶]	<0.0001	<0.0001

[a]Baseline data and during clinical trial and observational study years 1, 3, 4, 5, 6, and 7 follow-ups. Models are adjusted for age, education, race/ethnicity, occupation, marital status alcohol consumption, physical activity, family history of cancer, BMI, daily total energy intake and percentage of energy from fat, daily fruit consumption and daily vegetable consumption, and pack-year of smoking.
[b]Information on smoking was from baseline only.
[c]Information on smoking was from both baseline and follow-ups. New quitters were separate from baseline former smokers for analysis.
[d]Information on smoking was from both baseline and follow-ups. New quitters were combined with baseline former smokers for analysis.
[e]Trend test was performed among former smokers by treating the median values of each YSQ category as continuous variable in the multivariable adjusted Cox proportional hazard regression models.

pack-years of smoking (0.44 for model adjusted for cigarettes per day), indicating that there is no significant difference in smoking cessation and HR of bladder cancer across different subtypes.

Discussion

In this large prospective study among postmenopausal women, we found that smoking cessation was inversely associated with the risk of bladder cancer in

Table 4. Multivariate-adjusted HR of subtypes of bladder cancers in relation to smoking status

	Numbers of cases			Multi-adjusted HR (95% CI)[a]		
Variable	**Transitional**	**Papillary**	**Other types[b]**	**Transitional**	**Papillary**	**Other types[b]**
Never smoker (ref)	57	220	43	1.00	1.00	1.00
Former smoker (years since quitting smoking)	66	282	90	2.35 (1.56–3.54)	2.42 (1.99–2.94)	3.57 (1.86–6.87)
<10	15	57	21	2.98 (1.66–5.34)	2.65 (2.00–3.52)	4.71 (2.69–8.23)
10–<20	21	77	32	1.86 (1.05–3.31)	2.33 (1.80–3.02)	4.94 (2.72–7.11)
20–<30	15	82	17	2.95 (1.73–5.05)	2.53 (1.92–3.34)	2.04 (1.06–3.93)
≥30	15	66	20	1.88 (0.94–3.76)	1.87 (1.31–2.67)	2.22 (1.11–4.44)
Current smoker	16	82	14	3.66 (1.96–6.82)	3.91 (2.96–5.17)	5.45 (2.60–11.46)

[a]Adjusted for age, education, race/ethnicity, occupation, marital status alcohol consumption, physical activity, family history of cancer, BMI, daily total energy intake and percentage of energy from fat, daily fruit consumption and daily vegetable consumption, and pack-years.
[b]Including squamous cell carcinoma, adenocarcinoma, and other types, which include adenocarcinoma, squamous cell carcinoma, small cell carcinoma, lymphoepithelial carcinoma, hemangiosarcoma, clear cell adenocarcinoma, and undifferentiated carcinoma.

comparison with current smokers. Models using baseline data showed that after taking into account pack-years of smoking, the most rapid decrease occurred in the first 10 YSQ, with risk dropping by 25%. The risk of bladder cancer continued decreasing after 10 YSQ but remained substantially elevated relative to never smokers by 1.92 times even after 30 years of cessation. Results from models that used time-updated information on smoking showed a similar pattern. In comparison with women who continued to smoke, those who quit smoking during follow-ups had a 39% decline in risk of bladder cancer, and the risk continued to drop with greater YSQ. We found similar patterns in results of subtypes of bladder cancer.

The relationship between smoking and risk of bladder cancer has been well-established by previous studies conducted in both genders (16, 17, 20, 22, 25). Nevertheless, the magnitude of risk reduction among former smokers has remained controversial. Some studies suggested that former smokers have elevated risks of bladder cancer in comparison with never smokers by approximately 2-fold (10). A systematic review of eight case–control studies found that bladder cancer risk was up to 3 times higher for former smokers relative to never smokers (39). Three large prospective studies reported bladder cancer risk among former smokers were 2.00 to 2.25 times higher in comparison with never smokers (10, 22, 40). When adjusted for pack-years of smoking or number of cigarettes per day, our study confirmed that among postmenopausal women, there was a 2.57 to 2.77 times elevated risk of bladder cancer among former smokers compared with never smokers. After quitting smoking, in comparison with current smokers, former smokers experience a 25% decrease in risk of bladder cancer over 10 YSQ, which continues to decrease with greater YSQ.

Findings on whether the risk of bladder cancer of former smokers can decrease to the level of never smokers also remained inconsistent in studies conducted in the general population (18, 22, 39, 41). Some studies suggested that the risk of bladder cancer among former smokers decreased to close to never smokers after more than 20 years of quitting (17, 19, 20). However, other studies indicated that the bladder cancer risk decreased as YSQ increased, but the risk remained elevated after quitting smoking for more than 20 years (8, 16, 21, 22, 40). Results from our multivariable-adjusted model (Model 2) showed that there was no statistically significant difference in risk of bladder cancer between former smokers who quit smoking for 30 years or more and never smokers. However, after further adjusting for numbers of cigarettes per day (Model 3) or pack-years of smoking (Model 4), the risk of bladder cancer in former smokers remained significantly higher than that of never smokers even after 30 or more YSQ. This change in results suggests that smoking intensity and duration should be taken into account when analyzing the smoking–bladder cancer association (16).

The dose–response relationship between YSQ and risk of bladder cancer was examined by previous studies in both men and women. One study suggested an approximate dose–response trend between YSQ and reduction in risk of bladder cancer (17), and other studies found that the decrease in bladder cancer risk occurred within the first 2 to 5 YSQ, then slowed down as YSQ increased (8, 18, 41, 42). We observed that among postmenopausal women who were former smokers, there was a significantly lower risk of bladder cancer compared with current smokers, with the most rapid reduction in the first 10 YSQ. The risk continued to decrease after the first 10 YSQ among former smokers, but did not follow a dose–response pattern for all time periods.

The biological mechanisms of the association between smoking and bladder cancer remain unclear. Some studies suggested that findings from smoking and bladder cancer risks can be connected with models of tobacco-related carcinogenesis in lung cancer and other smoking-related cancers, which suggested that the exposure of long-term smoking persistently facilitates DNA adducts by interfering with apoptosis and affecting the repair procedure (43). Long-term exposure to the myriad components of cigarette smoke, including aromatic amines, facilitates the formation of DNA adducts and induces mutations in primary cancer-related genes such as the RUNX3 and IGF2-H19 loci in immortalized urothelial cells. Hypomethylation at these sites, in turn, prompts the process of carcinogenesis (43, 44). Recent studies suggested that exposure to smoking may be involved in tumorigenesis at early stages (30, 44). The genotoxic effects of smoking are considered to be the most important effects given its role in early stages of carcinogenesis and high-frequency occurrence. This early stage effect may explain our findings on remaining elevated hazard risk of bladder cancer among former smokers compared with never smokers, even after many YSQ (45).

We found similar associations between YSQ and risks of papillary and transitional bladder cancers, which is also consistent with findings from previous studies conducted in the general population (30, 43). Findings of several previous studies suggest that the association between age of smoking initiation, duration of smoking, and the risk of bladder cancer was stronger in invasive bladder cancer subtypes in comparison with noninvasive subtypes (25, 30, 31). For example, people who started smoking at an early age or smoked for longer duration were more likely to develop more invasive subtypes, such as basal-like bladder cancers rather than luminal-like cancers (30). Smoking cessation is found to be associated with reduction of all subtypes of bladder cancer. The magnitude of reduction is more prominent among

superficial bladder cancer than muscle-invasive cancer (25). Our finding on bladder cancer subtypes indicated that for both transitional and papillary bladder cancers, the HRs decreased with greater YSQ, but even after quitting smoking for 30 years, HRs of both subtypes remained higher among former smokers in comparison with never smokers.

The strengths of our study include using data from a large prospective cohort of postmenopausal women, with participants from wide-spread geographical areas. This study provides information on a population that has been understudied in terms of smoking and also of bladder cancer. We included detailed information on exposure as well as potential confounders. The confirmation of cases was by trained adjudicators according to standard cancer codes. However, there are limitations of our study. First of all, the small numbers of cases for subtypes of bladder cancer restricted our analysis on associations between smoking cessation and risks of other subtypes of bladder cancer. However, according to a Surviellance, Epidemiology, and End Results (SEER) Program report, papillary and transitional cell carcinomas comprise 90% to 95% of all bladder cancers, which implied that our findings still have public health significance (36). Secondly, the smoking prevalence in the whole U.S. population is 15.1% (46). The prevalence of smoking in the WHI is 6.9%, which is close to the prevalence of smoking among people who are 65 and older reported by Centers for Disease Control and Prevention (CDC), but still smaller than the prevalence of the whole population. This difference may attenuate the generalizability of our findings.

In conclusion, by using a large prospective cohort study of postmenopausal women, we found that in comparison with women who currently smoke, former smokers experienced a 25% decrease in risk of bladder cancer within 10 YSQ, and this risk continued to decrease with greater YSQ, though remained higher than that of never smokers after 30 or more YSQ. Thus, older women who smoke should be advised to quit smoking in order to reduce their bladder cancer risk. The study indicates the importance of primary prevention as well as the importance of smoking cessation. Further studies examining the underlying mechanisms of relationships between smoking and bladder cancer, and studies exploring the relationships between smoking cessation and other subtypes of bladder cancer are likely to further our understanding of this issue.

Disclosure of Potential Conflicts of Interest

H.A. Tindle is a consultant/advisory board member for Achieve Life Sciences and received donated smoking cessation medications from manufacturer. No potential conflicts of interest were disclosed by the other authors.

Disclaimer

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Writing, review, and/or revision of the manuscript: Y. Li, H.A. Tindle, M.S. Hendryx, P. Xun, K. He, X. Liang, J. Luo
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): Y. Li
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