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Original Contribution

A Prospective Cohort Study of Bladder Cancer Risk in Relation to Active Cigarette Smoking and Household Exposure to Secondhand Cigarette Smoke

Anthony J. Alberg[1], Anthony Kouzis[1], Jeanine M. Genkinger[2], Lisa Gallicchio[1], Alyce E. Burke[1], Sandra C. Hoffman[1], Marie Diener-West[3], Kathy J. Helzlsouer[1], and George W. Comstock[1]

[1] Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD.
[2] Department of Nutrition, Harvard School of Public Health, Boston, MA.
[3] Department of Biostatistics, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD.

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Active cigarette smoking is a major risk factor for bladder cancer. Secondhand exposure to cigarette smoke may also contribute to bladder carcinogenesis. The authors conducted a prospective cohort study to examine the influence of both active smoking and household exposure to secondhand smoke (SHS) on subsequent bladder cancer risk. The study population included persons from two cohorts established from private censuses conducted in Washington County, Maryland, in 1963 ($n = 45{,}749$; 93 cases) and 1975 ($n = 48{,}172$; 172 cases). Poisson regression models were fitted to estimate the relative risk of bladder cancer associated with active and passive smoke exposure in the two cohorts (referent category: never smokers who did not live with any smokers). Current smokers had an elevated risk of bladder cancer in both the 1963 cohort (relative risk (RR) = 2.7, 95% confidence limits (CL): 1.6, 4.7) and the 1975 cohort (RR = 2.6, 95% CL: 1.7, 3.9) after adjustment for age, education, and marital status. Among nonsmoking women, current household SHS exposure was associated with bladder cancer risk in the 1963 cohort (RR = 2.3, 95% CL: 1.0, 5.4) but not in the 1975 cohort (RR = 0.9, 95% CL: 0.4, 2.3). This study further solidifies the evidence that active smoking is causally associated with bladder cancer. Additional studies are needed to determine whether passive smoking is a risk factor for bladder cancer.

bladder neoplasms; risk factors; smoking; tobacco smoke pollution

Abbreviations: CL, confidence limits; RR, relative risk.

On the basis of an extensive body of scientific evidence, active cigarette smoking has been considered to be causally associated with bladder cancer for more than 15 years (1). The evidence to support a causal association is based on over 30 case-control studies (2) and a smaller number of prospective cohort studies (3–11). A pooled analysis of data from case-control studies indicated an approximately 3.5-fold elevated risk among current smokers versus never smokers in both men and women (12). The evidence from cohort studies has been remarkably consistent in indicating a twofold or greater excess risk of developing or dying from bladder cancer among current smokers compared with never smokers (3–11), with risks in former smokers being intermediate between the risks of current and never smokers (5, 6, 8–11). A meta-analysis of observational epidemiologic studies estimated that, compared with never smokers, the risk of urinary tract (primarily bladder) cancer was elevated more than threefold among current smokers and twofold among former smokers (2). Active cigarette smoking is a major contributor to the population burden of bladder cancer, accounting for approximately 45 percent of all bladder cancer diagnoses (13). To augment the already extensive evidence from case-control studies, additional evidence from large cohort studies is valuable for more precisely characterizing the risks of

Reprint requests to Dr. Anthony J. Alberg, Department of Biostatics, Bioinformatics, and Epidemiology, Hollings Cancer Center, Medical University of South Carolina, 86 Jonathan Lucas Street, P.O. Box 250955, Charleston, SC 29425 (e-mail: alberg@musc.edu).

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active cigarette smoking and strengthening the overall foundation for making the claim of a causal association.

The causal relation between active cigarette smoking and bladder cancer provides reason to suspect that secondhand cigarette smoke (also known as environmental tobacco smoke or passive smoke) may also contribute to bladder carcinogenesis. As with active cigarette smoking, secondhand cigarette smoke contains arylamines, which are established bladder carcinogens (14). The dose of carcinogen exposure from secondhand smoke is less than that from active cigarette smoking, but even so, the relatively low dose of carcinogens from secondhand smoke exposure has been hypothesized to make a disproportionately large contribution to bladder carcinogenesis (14). This is because, among persons exposed to cigarette smoke, those who are genetically more susceptible to tobacco toxins are hypothesized to have greater bladder cancer risks in general but also risks that are disproportionately higher at low levels of exposure (14). The plausibility of an association between secondhand smoke and bladder cancer is further strengthened by the fact that carcinogens have been measured in the urine of passive smokers (15, 16), showing that carcinogens from secondhand smoke come into direct contact with the bladder.

The hypothesis that secondhand smoke exposure is a risk factor for bladder cancer has only rarely been explored in epidemiologic studies, despite the established link between active cigarette smoking and bladder cancer and a strong rationale for suspecting that secondhand cigarette smoke exposure could contribute to bladder carcinogenesis. The currently available epidemiologic evidence addressing this topic appears to be limited to case-control studies published in the 1980s (17–19) and one prospective cohort study (20). To further test the hypothesis that active and passive smoking both contribute to bladder carcinogenesis, we conducted a community-based, prospective cohort study to evaluate the influence of active cigarette smoking and household exposure to secondhand smoke on the risk of developing bladder cancer.

MATERIALS AND METHODS

Study population

This study was approved by the institutional review board of the Johns Hopkins Bloomberg School of Public Health (Baltimore, Maryland). The present study was based on two cohorts established when records were collected in two private censuses of the residents of Washington County, Maryland. The first census was conducted in 1963, and the second census was conducted in 1975. Specific details of the data collection methods are presented elsewhere (21). In each census, data on age, marital status, and years of education were collected for each household member. In addition, information on tobacco use was collected for all adults in the household. Approximately 98 percent of households (n = 91,909) in Washington County participated in the 1963 census, and 90 percent (n = 90,225) of county households participated in the 1975 census.

Participants were excluded from this analysis if they were younger than 25 years of age at the census date, had a prior cancer diagnosis, were pipe or cigar smokers only, or were missing information on age, gender, or smoking status. For the present study, the analytic cohorts comprised 45,749 participants in the 1963 cohort and 48,172 participants in the 1975 cohort. The 1963 cohort was followed for first-time occurrences of bladder cancer from 1963 to 1978; the 1975 cohort was followed from 1975 to 1994.

Exposure measurement

Information on smoking habits was ascertained using questionnaires administered to census participants in 1963 and 1975. In 1963, data collected on cigarette smoking habits consisted of current and former use of cigarettes among household members, the age at initiation of smoking for each household member who smoked, and the number of cigarettes smoked per day ($\leq$10, 11–20, or $>$20). In 1975, questions regarding cigarette smoking habits were similar to those administered in 1963; however, in 1975, the actual number of cigarettes smoked per day was recorded and the age at initiation of cigarette smoking was not.

Collection of smoking information on all household members directly provided the data with which to investigate active cigarette smoking habits and, by determining whether a never smoker resided with a cigarette smoker, a measure of household exposure to secondhand smoke. Respondents classified their active cigarette smoking status into one of three categories: never, former, or current smoking. Among current smokers, the amount smoked per day was categorized as $\leq$10, 11–20, or $>$20 cigarettes per day. Household exposure to secondhand smoke was considered positive if any household member other than that person was a current cigarette smoker. To account for never smokers who lived with a former smoker but not with any current smokers, secondhand smoke exposure was also classified into three categories as never, former, or current exposure.

Outcome measurements

After the baseline data collection established the two cohorts, the cohorts were followed up for the occurrence of invasive bladder cancer (*International Classification of Diseases*, Ninth Revision, code 188) using the Washington County Cancer Registry. This local registry ascertains cancer cases using death certificates and discharge records from Washington County Hospital, the only general hospital in the county. Comparison of case ascertainment by means of the Washington County Cancer Registry as compared with the Maryland Cancer Registry suggests that the county registry has been at least as complete as the state registry. In the present analyses, the number of bladder cancer cases diagnosed was 93 in the 1963 cohort, based on follow-up from 1963 to 1978, and 172 in the 1975 cohort, based on follow-up from 1975 to 1994.

Person-time of follow-up

A 5 percent random sample of each cohort was surveyed 8 (1963 cohort) or 10 (1975 cohort) years after the baseline data were collected, to determine what factors were associated with the probability of remaining alive and in

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Washington County. The follow-up survey for the 1963 cohort was conducted in July 1971, and the follow-up survey for the 1975 cohort was implemented in July 1985. The survey data were analyzed to characterize the probability of remaining a Washington County resident. Factors associated with emigration and death, such as age, gender, marital status, education, and smoking status, were included in a linear regression model to assign the probability of remaining a resident of the county.

The probability factor calculated for each person from this regression model was then multiplied by the maximum possible follow-up time for each cohort (15 years for the 1963 cohort and 19 years for the 1975 cohort) to estimate person-time, correcting for the potential for emigration as determined by individual characteristics (age, marital status, education, and smoking status). The maximum duration of follow-up was taken to be the period from the census date to July 15, 1978, for the 1963 cohort and the period from the census date to July 15, 1994, for the 1975 cohort. The rationale for truncating follow-up time at these dates was to stay within a time period in which the follow-up survey information could reasonably be expected to retain validity, by taking the follow-up survey date as the midpoint of the maximum follow-up interval. For example, in the 1975 cohort, each participant's follow-up time was calculated as the amount of time from baseline (July 15, 1978) to the end of his or her person-time, estimated by multiplying the probability of residing in the county by 19 years, the maximum follow-up interval. For a diagnosis of bladder cancer to contribute to the numerator of the incidence rate, the diagnosis had to occur during the participant's estimated follow-up time.

Statistical analyses

Poisson regression models (22) were employed to estimate the relative risks of developing bladder cancer among former and current smokers and participants exposed to passive smoke as compared with persons who had never actively smoked and who did not reside with any smokers. Relative risks were calculated with adjustment first for age and then for age, education, and marital status. All statistical analyses were performed using SAS (SAS Institute, Inc., Cary, North Carolina).

Each analytic cohort was analyzed separately. The entire analytic cohorts were included in analyses of the association between active cigarette smoking and bladder cancer. In these analyses, the relative risks were similar for men and women, and therefore both genders were combined. Analyses of the association between secondhand smoke exposure and bladder cancer were limited to never smokers, with participants who resided with at least one smoker being classified as exposed as compared with those from households with no smokers. Analyses were also carried out with secondhand smoke exposure classified as never, former, and current exposure, to account for persons who lived with a former smoker but not with any current smokers. Furthermore, only the results for women are presented, because so few cases of bladder cancer occurred among nonsmoking men exposed to secondhand smoke ($n = 3$).

TABLE 1. Characteristics of two cohorts established in 1963 and 1975 when records were collected in two private censuses of the residents of Washington County, Maryland

Variable	1963 cohort		1975 cohort	
	No.	%	No.	%
Total	45,749	100.0	48,172	100.0
Gender				
Male	20,926	45.7	21,791	45.2
Female	24,823	54.3	26,381	54.8
Age (years)				
25–34	10,115	22.1	11,814	24.5
35–44	11,875	26.0	9,443	19.6
45–54	9,957	21.8	10,140	21.0
55–64	7,059	15.4	8,382	17.4
≥65	6,743	14.7	8,393	17.4
Education (years)				
<12	26,997	59.0	20,980	43.6
≥12	17,652	38.6	26,544	55.1
Missing data	1,100	2.4	648	1.3
Marital status				
Married	36,139	79.0	37,649	78.2
Widowed	4,431	9.7	4,883	10.1
Divorced/separated	2,949	6.4	2,871	6.0
Single	2,085	4.6	2,710	5.6
Missing data	145	0.3	59	0.1
Smoking status				
Never an active smoker, no secondhand smoke exposure	11,722	25.6	15,249	31.7
Secondhand smoke exposure only	7,117	15.6	4,932	10.2
Former smoker	6,873	15.0	10,985	22.8
Current smoker	20,037	43.8	17,006	35.3

RESULTS

The characteristics of the 1963 and 1975 cohorts are summarized in table 1. The two cohorts did not differ significantly with regard to the demographic characteristics presented. Reflecting the population of Washington County, almost all of the participants were Caucasian.

In the 1963 cohort, 44 percent were current smokers, 15 percent were former smokers, 16 percent were nonsmokers who lived with smokers, and 26 percent were never smokers who did not live with any smokers (table 1). This distribution changed in 1975, with a lower prevalence of current smoking (35 percent) and exposure to secondhand smoke (10 percent) but a higher percentage of former smokers (23 percent) and nonsmokers who did not live with smokers (32 percent). In both cohorts, women were less likely than men to be active smokers and more likely to be exposed to secondhand smoke at home (table 2).

Current active cigarette smokers had a greater than 2.5-fold increased risk of bladder cancer in both the 1963 and

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TABLE 2. Characteristics (numbers and row percentages) of members of two cohorts established from private censuses conducted in 1963 and 1975, by smoking status, Washington County, Maryland

	Never an active smoker, no secondhand smoke exposure	Secondhand smoke exposure only	Former smoker	Current smoker
	1963 cohort ($n = 45,749$)			
Total no.	11,722	7,117	6,873	20,037
Gender				
Male	15.2	4.4	22.4	58.0
Female	34.5	24.9	8.8	31.8
Age (years)				
25–34	20.1	13.7	12.9	53.3
35–44	18.3	14.0	15.2	52.5
45–54	20.3	16.2	16.2	47.3
55–64	31.3	16.7	16.2	35.8
≥65	48.8	18.9	14.9	17.4
Marital status				
Married	22.3	15.4	16.4	45.9
Widowed	48.0	20.8	9.3	21.9
Divorced/ separated	38.0	13.6	9.6	38.8
Single	19.0	10.2	11.3	59.5
Education (years)				
<12	26.2	16.6	13.9	43.3
≥12	24.6	13.9	16.7	44.8
	1975 cohort ($n = 48,172$)			
Total no.	15,249	4,932	10,985	17,006
Gender				
Male	19.9	4.0	32.8	43.3
Female	41.4	15.4	14.5	28.7
Age (years)				
25–34	28.8	10.8	18.6	41.8
35–44	26.0	10.9	21.5	41.6
45–54	24.7	10.3	24.7	40.3
55–64	32.0	8.6	27.1	32.3
≥65	50.1	10.3	23.7	15.9
Marital status				
Married	28.5	10.4	24.9	36.2
Widowed	53.1	11.1	15.1	20.7
Divorced/ separated	42.9	11.4	14.5	31.2
Single	25.2	5.0	16.9	52.9
Education (years)				
<12	31.6	10.5	21.2	36.7
≥12	31.7	10.0	24.1	34.2

1975 cohorts (table 3). Compared with the referent category of never smokers from households with no smokers, the relative risks for current cigarette smokers after adjustment for age, education, and marital status were 2.7 (95 percent confidence limits (CL): 1.6, 4.7) and 2.6 (95 percent CL: 1.7, 3.9) in the 1963 and 1975 cohorts, respectively. Among current smokers, the tests for trend of increasing risk with increased number of cigarettes smoked per day were statistically significant in both the 1963 ($p < 0.001$) and 1975 ($p < 0.001$) cohorts. Former smokers did not have a statistically significant excess risk of bladder cancer in the 1963 cohort (adjusted relative risk (RR) = 1.2, 95 percent CL: 0.5, 2.5); this finding was based on only 11 bladder cancer cases in the exposed group. In contrast, based on a more substantial number of bladder cancer diagnoses among former smokers in the 1975 cohort ($n = 57$), an increased risk of bladder cancer that was almost as strong as that for current active smoking was observed (adjusted RR = 2.3, 95 percent CL: 1.5, 3.4).

Among women in the 1963 cohort who were never active smokers, those with current household secondhand smoke exposure had a greater than twofold increase in the risk of developing bladder cancer in comparison with women who were not currently exposed, after adjustment for age, education, and marital status (RR = 2.3, 95 percent CL: 1.0, 5.4) (table 4). When household secondhand smoke exposure was classified to further account for former exposure as well as current exposure, the relative risk for current secondhand smoke exposure versus never secondhand smoke exposure was weaker and no longer statistically significant (table 4). In contrast to the elevated risk seen in the 1963 cohort, in the 1975 cohort current secondhand smoke exposure was not associated with an increased risk of bladder cancer among nonsmoking women (RR = 0.9, 95 percent CL: 0.4, 2.3) (table 4). There was no dose-response trend in the relative risks when results were evaluated by the cumulative number of cigarettes smoked per day by the smokers in the household (data not shown).

DISCUSSION

This long-term, community-based prospective cohort study was carried out to assess the influence of active cigarette smoking and household exposure to secondhand cigarette smoke on the risk of bladder cancer. Exposure to secondhand smoke was not a suspected risk factor for cancer in the 1960s, so it is rare for a cohort study initiated during that era to have the capacity to investigate secondhand smoke exposure. The fact that two private censuses established two cohorts also allowed us to examine the associations between cigarette smoke exposure and bladder cancer during two different time periods, 1963–1978 and 1975–1994. The findings for these two time points were consistent in showing an approximately 2.5-fold increase in the risk of bladder cancer associated with active cigarette smoking. The associations for active cigarette smoking and bladder cancer risk were consistent in both men and women.

The magnitude of the associations in our study is in keeping with the relative risk estimates seen in many other cohorts (4, 5, 7, 9). In the present study, even though a statistically significant trend was observed, the relative risks did not increase along a consistent, monotonic gradient

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TABLE 3. Relative risk of developing bladder cancer according to active cigarette smoking status, Washington County, Maryland, 1963–1978 and 1975–1994

Smoking status	1963 cohort						1975 cohort					
	No. of cases	Person-years	RR*,†	95% CL*	RR‡	95% CL	No. of cases	Person-years	RR†	95% CL	RR‡	95% CL
Never an active smoker, no current secondhand smoke exposure§	20	134,243	1.0		1.0		40	223,063	1.0		1.0	
Current secondhand smoke exposure only	14	84,119	1.5	0.8, 3.0	1.4	0.7, 2.7	8	73,183	0.8	0.4, 1.8	0.8	0.4, 1.7
Former smoker	11	81,852	1.4	0.7, 3.0	1.2	0.5, 2.5	57	144,156	2.5	1.6, 3.7	2.3	1.5, 3.4
Current smoker	48	239,377	3.1	1.8, 5.3	2.7	1.6, 4.7	67	221,944	2.8	1.9, 4.2	2.6	1.7, 3.9
Current amount smoked (cigarettes/day)¶												
≤10	7	47,111	1.8	0.8, 4.4	1.7	0.7, 4.1	11	22,878	2.4	1.5, 3.9	2.2	1.4, 3.6
11–20	28	119,803	3.8	2.1, 6.8	3.2	1.7, 5.9	34	125,638	3.7	1.9, 7.3	3.3	1.7, 6.7
>20	12	68,480	3.2	1.5, 6.7	2.9	1.4, 6.1	20	66,384	3.5	2.0, 6.1	3.3	1.9, 1.7

* RR, relative risk; CL, confidence limits.
† Adjusted for age.
‡ Adjusted for age, education, and marital status.
§ Referent category.
¶ Because of missing information on the number of cigarettes smoked per day, numbers of cases for this variable sum to less (by one in the 1963 cohort and two in the 1975 cohort) than the total numbers of cases who were current smokers.

according to the number of cigarettes smoked per day. This finding is similar to those of a number of studies (3, 5, 9), but some other studies have observed a consistent dose-response gradient (7, 8). Some of the previous cohort studies were based on fewer bladder cancer cases (3, 7–10) and measured bladder cancer mortality rather than incidence (3–7). The present findings further solidify the conclusion that active cigarette smoking is a major cause of bladder

TABLE 4. Relative risk of developing bladder cancer according to secondhand exposure to household cigarette smoke among women who were never active smokers, Washington County, Maryland, 1963–1978 and 1975–1994

SHS* exposure	1963 cohort						1975 cohort					
	No. of cases	Person-years	RR*,†	95% CL*	RR‡	95% CL	No. of cases	Person-years	RR†	95% CL	RR‡	95% CL
Current SHS exposure versus noncurrent SHS exposure												
No current SHS exposure§	10	97,221	1.0		1.0		24	162,130	1.0		1.0	
Current SHS exposure	13	73,506	2.6	1.1, 6.0	2.3	1.0, 5.4	6	61,194	1.0	0.4, 2.5	0.9	0.4, 2.3
Current and former SHS exposure versus never SHS exposure												
Never SHS exposure§	9	66,576	1.0		1.0		17	107,375	1.0		1.0	
Former SHS exposure	1	30,645	0.3	0.1, 2.8	0.3	0.1, 2.5	7	54,756	1.1	0.5, 2.6	0.8	0.3, 2.0
Current SHS exposure	13	73,506	2.2	0.9, 5.2	1.8	0.8, 4.5	6	61,194	1.0	0.4, 2.7	0.9	0.3, 2.2
Source of SHS exposure¶												
Spouse only	5	45,318	1.8	0.6, 5.5	1.1	0.3, 3.8	5	40,369	1.7	0.6, 4.9	1.2	0.4, 3.6
Other household member only	8	19,682	3.0	1.2, 7.8	3.0	1.2, 7.9	1	15,603	0.4	0.1, 3.0	0.4	0.1, 3.3

* SHS, secondhand smoke; RR, relative risk; CL, confidence limits.
† Adjusted for age.
‡ Adjusted for age, education, and marital status.
§ Referent category.
¶ The "spouse plus other household member" category did not contain any bladder cancer cases.

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cancer (1). These findings also indicate that the study had strong internal validity. Consistent with most previous cohort studies that have reported relevant data (5, 6, 8–11), former smokers had a substantially elevated risk of bladder cancer in the 1975 cohort. In the 1963 cohort, the small number of bladder cancer cases among former smokers limited our ability to assess the association with an adequate degree of statistical precision.

Among women, results from the two cohorts diverged with respect to the potential contribution of household secondhand smoke exposure and bladder cancer risk. Evidence of an association between secondhand smoke exposure and bladder cancer risk was observed in the 1963 cohort, but no increased risk was observed in the 1975 cohort. In both cohorts, only three cases in total were observed among nonsmoking men exposed to secondhand smoke at home, so our inferences for secondhand smoke exposure are limited to women.

The reason for the discrepancy in results for secondhand smoke exposure among women across the two time points is not clear. The degree of exposure to smoking in the household does not provide a viable explanation, as the median exposure was greater in the 1975 cohort (20 cigarettes/day) than in the 1963 cohort (15 cigarettes/day). If the observed associations are true, one possible explanation for the difference between the associations observed in 1963 and 1975 could be that our measurement of secondhand smoke exposure was limited to exposure at home. The relative importance of secondhand smoke exposure at home probably decreased over time because the proportion of women working outside of the home increased markedly during the years in which these studies took place (23). Chance remains a possible explanation, but if this is the case, it is unclear whether the results for the 1963 cohort are false-positive or the results for the 1975 cohort are false-negative.

Compared with the abundance of previous evidence on active smoking and bladder cancer, only scant evidence is available to compare with the secondhand smoke findings. In previously published studies, the associations observed between secondhand smoke exposure and bladder cancer have been variable, but to our knowledge no association as clear-cut and strong as the one we observed in the 1963 cohort have been previously noted. Odds ratios calculated from the data presented by Kabat et al. (17), from a case-control study comprising 84 bladder cancer cases and 266 controls who were all nonsmokers, show some odds ratios pointing in the direction of increased risk and others pointing in the protective direction. Specifically, the odds ratios were 1.5 (95 percent CL: 0.4, 5.3) for men and 0.6 (95 percent CL: 0.2, 2.6) for women for any exposure to secondhand smoke at home, versus none; 0.8 (95 percent CL: 0.4, 1.6) for men and 1.2 (95 percent CL: 0.5, 12.7) for women for spousal smoking; and 0.6 (95 percent CL: 0.2, 2.0) for men and 2.5 (95 percent CL: 0.5, 12.7) for women for any exposure to secondhand smoke at the workplace or during transportation, versus none (17). In a case-control study that included 142 bladder cancer cases and 217 controls who were not current active smokers, none of the odds ratios pointed in the direction of increased risk for either men or women for secondhand smoke exposure at home or at work (18). In a case-control study that included six cases of urinary tract cancer, the adjusted odds ratio for secondhand smoke exposure was 1.1 (95 percent CL: 0.2, 7.6) (19).

Prospective data have been previously reported. In a case-cohort study of 619 persons who developed bladder cancer and 3,346 cohort members who did not develop cancer, Zeegers et al. (20) found, after adjusting for numerous factors (including age, sex, dietary factors, occupation, and family history), that the relative risks of bladder cancer were 0.7 (95 percent CL: 0.3, 1.9), 1.2 (95 percent CL: 0.6, 2.4), 1.4 (95 percent CL: 0.7, 2.6), and 0.6 (95 percent CL: 0.3, 1.4) among persons who lived with a currently smoking partner, had a smoking parent, were exposed to secondhand smoke at work, or had 3 or more hours of secondhand smoke exposure per day, respectively, as compared with persons not exposed to secondhand smoke. Considered in total, the results of previous studies seem to be more compatible with the null findings we observed among women in the 1975 cohort.

Despite the advantages of the present investigation, a number of limitations should be considered when assessing the evidence provided by this study, particularly with respect to secondhand smoke exposure. First, even though two cohorts of substantial size were followed up for 15 or more years, the number of bladder cancer cases diagnosed in the group exposed to secondhand smoke was small—14 in the 1963 cohort and eight in the 1975 cohort—limiting the precision of the estimated relative risks. Second, our measure of secondhand smoke exposure was limited in several ways. It focused solely on exposure at home, and thus did not account for secondhand smoke exposure that occurred in the workplace or during leisure time outside the home. Thus, persons who were considered nonexposed on the basis of our measure of household exposure may actually have been exposed to secondhand smoke in one or more of these venues. If there is a true association between secondhand smoke exposure and bladder cancer, the net result of this misclassification would have been to bias the relative risks toward the null. The secondhand smoke exposure measure used in the present study was limited to adulthood exposure; to the extent that childhood secondhand smoke exposure is related to bladder cancer risk, this would exacerbate the problem mentioned above. Secondhand smoke exposure in this study was measured at the beginning of a long-term prospective cohort study, and thus the findings did not account for changes in secondhand smoke exposure that may have occurred during follow-up. If secondhand smoke exposure contributes to bladder cancer risk, it is likely to exert a small effect. For a weak association, these potential biases toward the null could collectively prevent a true association from being observed. For these reasons, the results of this study should be considered hypothesis-generating.

We also did not collect data on other known or suspected risk factors for bladder cancer, such as occupational exposure to bladder carcinogens (24). It is difficult to predict how the distributions of these variables might have differed according to cigarette smoke exposure and, hence, acted to confound the associations observed in the present study. Even though more complete information would have been desirable, one measure of the study's internal validity is that

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the observed associations for active smoking pointed in the direction expected based on previous research. The 2004 Surgeon General's report (1) noted that there are no likely confounders of the association with active smoking, but the possibility of confounding when studying exposure to secondhand smoke may be more problematic.

In summary, the results of this large, community-based prospective cohort study provide further confirmation of the important role that active cigarette smoking plays in the etiology of bladder cancer. The marked elevation in risk associated with active smoking provides additional data which further support the evidence that smoking causes bladder cancer. With respect to the hypothesis that secondhand smoke exposure contributes to the risk of bladder carcinogenesis, the results of the present study were mixed. In women, the results for the 1963 cohort provided strong evidence linking secondhand smoke exposure to the risk of developing bladder cancer, but this evidence was counterbalanced by the null results observed in the 1975 cohort. Whether a genuine association exists between secondhand smoke exposure and bladder cancer remains an open question. There is a strong biologic rationale to support the hypothesis, but the present uncertainty of the epidemiologic evidence, combined with the public health importance of this issue, justifies carrying out additional studies to determine whether or not secondhand smoke exposure is truly associated with bladder cancer risk.

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Conflict of interest: none declared.

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