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ORIGINAL REPORT

Cigarette Smoking Prior to First Cancer and Risk of Second Smoking-Associated Cancers Among Survivors of Bladder, Kidney, Head and Neck, and Stage I Lung Cancers

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ABSTRACT

Purpose
Data on smoking and second cancer risk among cancer survivors are limited. We assessed associations between smoking before first cancer diagnosis and risk of second primary smoking-associated cancers among survivors of lung (stage I), bladder, kidney, and head/neck cancers.

Methods
Data were pooled from 2,552 patients with stage I lung cancer, 6,386 with bladder cancer, 3,179 with kidney cancer, and 2,967 with head/neck cancer from five cohort studies. We assessed the association between prediagnostic smoking and second smoking-associated cancer risk with proportional hazards regression, and compared these estimates to those for first smoking-associated cancers in all cohort participants.

Results
Compared with never smoking, current smoking of ≥ 20 cigarettes per day was associated with increased second smoking-associated cancer risk among survivors of stage I lung (hazard ratio [HR] = 3.26; 95% CI, 0.92 to 11.6), bladder (HR = 3.67; 95% CI, 2.25 to 5.99), head/neck (HR = 4.45; 95% CI, 2.56 to 7.73), and kidney cancers (HR = 5.33; 95% CI, 2.55 to 11.1). These estimates were similar to those for first smoking-associated cancer among all cohort participants (HR = 5.41; 95% CI, 5.23 to 5.61). The 5-year cumulative incidence of second smoking-associated cancers ranged from 3% to 8% in this group of cancer survivors.

Conclusion
Understanding risk factors for second cancers among cancer survivors is crucial. Our data indicate that cigarette smoking before first cancer diagnosis increases second cancer risk among cancer survivors, and elevated cancer risk in these survivors is likely due to increased smoking prevalence. The high 5-year cumulative risks of smoking-associated cancers among current smoking survivors of stage I lung, bladder, kidney, and head/neck cancers highlight the importance of smoking cessation in patients with cancer.

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INTRODUCTION

Approximately one in six cancers diagnosed occurs among the 13 million cancer survivors living in the United States[1] Although cigarette smoking is a strong, modifiable risk factor for a number of malignancies,[2] continued use of tobacco after an initial diagnosis of a smoking-associated cancer is common.[3-6] Cancer sites strongly related to smoking and/or alcohol consumption make up more than one third of all second primary malignancies in the United States, and survivors of smoking-associated cancers are at increased risk of developing a second smoking-associated cancer, compared with the general population.[7] However, it is unclear whether the elevated risk of second smoking-associated cancers among survivors of first primary smoking-associated cancers is due to higher smoking prevalence among cancer survivors or to increased susceptibility to the effects of cigarette smoking.

Data on the association between smoking and second cancer risk in cancer survivors are limited, largely because registry-based studies lack information on cigarette smoking and other individual-level data, clinical trials generally lack detailed smoking

data, and cohort studies have limited numbers of second cancers. Among the few studies to investigate the association between smoking and second primary cancer risk, continued smoking after a lung cancer or head/neck cancer diagnosis has been associated with increased second primary cancer risk.[7-15] However, these studies were generally small and did not include survivors of other smoking-related cancers.

In the current study, we pooled data from five large, prospective epidemiologic cohorts to assess the association between prediagnostic (ie, collected on the baseline questionnaire before cancer diagnosis) smoking behaviors and second cancer risk among survivors of bladder, kidney, head/neck, and stage I lung cancers. To assess whether these survivors are more susceptible to the effects of tobacco, we compared these estimates with relative risks for smoking and first smoking-associated cancer risk.

METHODS

Study Population

The study population was derived from five prospective cohort studies: the National Institutes of Health (NIH)-AARP Diet and Health Study; the Agricultural Health Study (AHS); the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study; the Iowa Women's Health Study (IWHS); and the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial. Details regarding each study population and cohort design as well as a description of the pooling project have been published elsewhere.[16-21]

Cancers were ascertained either with linkage to population-based cancer registries or by self-report confirmed with medical record review. Individual studies utilized different versions of the International Classification of Diseases for Oncology (ICD-O) to classify cancers; therefore, we coded all cancers according to the SEER Program Incidence Site Recode based on ICD-*O*-3.[22,23] In this analysis, we included individuals with at least 30 days of follow-up, and incident, first primary diagnoses of bladder (ICD-*O*-3 site: C670-C679), kidney and renal pelvis (C649, C659), head/neck (C000-C009, C019-C0119, C129, C130-C140, C142-C148, C150-C159) and stage I lung cancers (C320-C329), excluding histology codes 9590 to 9989, 9050 to 9055 and 9140. These cancer sites were chosen due to their associations with cigarette smoking, prolonged survival relative to other smoking-associated cancers, and number of cases. The fraction of cases surviving 5 years after diagnosis for each smoking-related cancer site and hazard ratios (HRs) for the association between smoking status and first smoking-associated cancer diagnosis were assessed with data using the pooled cohorts. Cancer sites with 5-year survival less than 50% (eg, pancreas), fewer than 2,000 cases (eg, larynx), or weaker associations (relative risk < 2.0) with cigarette smoking (eg, colorectal) were not included in this analysis. Lung cancers were restricted to stage I tumors, based on SEER summary stage, to allow for sufficient survival.

Our primary analysis focused on the combined end point of second smoking-associated cancers, as defined by the International Agency for Research on Cancer (IARC), including cancers of the oral cavity, oropharynx, nasopharynx, hypopharynx, esophagus (adenocarcinoma/squamous cell carcinoma), stomach, colorectum, liver, pancreas, nasal cavity/paranasal sinuses, larynx, lung, uterine cervix, ovary (mucinous), urinary bladder, kidney (body/pelvis) and ureter, and myeloid leukemia.[2] To distinguish multiple reports, recurrence and metastases of the first primary malignancy from a second primary malignancy, we applied the SEER 2007 Multiple Primary and Histology Coding Rules,[24] and limited our analyses to non–same-site second primary malignancies.

Prediagnostic smoking parameters and other covariates collected at baseline were harmonized across the cohorts. Herein prediagnostic smoking refers to smoking before first cancer diagnosis. Each cohort had information on smoking status and cigarettes smoked per day. ATBC, AHS, PLCO and IWHS had data on pack-years smoked, and PLCO, IWHS and NIH-AARP had data on years since quitting among former smokers. Individuals without smoking status information at baseline were excluded from the analysis (n = 421).

Statistical Analysis

In separate models among survivors of stage I lung, bladder, kidney, and head/neck cancers, Cox proportional hazards regression was used to assess the association between prediagnostic smoking behaviors and second non–same-site smoking-associated cancer risk. Individuals were followed from their first primary cancer diagnosis to second cancer diagnosis, death or end of cohort follow-up. Same-site second cancers were censored at diagnosis date. All models used age as the underlying time scale, and were adjusted for sex, race (white, nonwhite, missing), education (high school diploma or less, vocational school/some college, college graduate/graduate school, missing), body mass index (< 25, 25-29.9, $30+$ kg/m^2), cohort, time from baseline to first cancer diagnosis (modeled continuously) and time since diagnosis of primary cancer (modeled as a polynomial spline).[25] Due to the relatively low proportion of individuals with missing data, we opted to add an additional category to variables (ie, missing value) as compared with more complicated imputation methods, because such methods would require additional assumptions and are unlikely to significantly change the results.[26] Complete cancer stage and alcohol use were not available from PLCO and ATBC, therefore in a sensitivity analysis limited to those cohorts with available data, we in addition adjusted for alcohol and stage, and found similar associations (data not shown). Of note, PLCO did collect stage on lung cancers and ATBC had more complete information for lung cancer stage, therefore we were able to restrict our analysis to stage I lung cancers, despite missing stage information for other cancer sites. Inferences remained the same when those with less than 30 days of follow-up were included (Appendix Table A1, online only).

In our main model, prediagnostic smoking was defined based on both smoking status and number of cigarettes smoked per day at baseline (never-smoker, former smoker < 20 cigarettes per day, former smoker ≥ 20 cigarettes per day, current smoker < 20 cigarettes per day, current smokers ≥ 20 cigarettes per day). This model excluded ATBC, as all participants in this cohort were current smokers at baseline. Additional models examined cigarettes per day among current smokers (all cohorts), pack-years smoked among ever smokers (excluding NIH-AARP), and years since quitting among former smokers (excluding AHS and ATBC). A trend across exposure categories was estimated by treating each categorical exposure as a continuous variable. Interactions by cohort were assessed with a cross-product term in the model.

We carried out several sub-analyses. First, to address the impact that deaths shortly after first primary cancer diagnosis have on our results, we restricted our analysis to 3-year survivors. Next, head/neck cancers were stratified by primary site (oral cavity, oropharynx, other head/neck, and larynx). In addition, stratified by primary cancer site, we assessed the association between smoking status and cigarettes per day with death.

Further, we compared the association between cigarette smoking and second primary smoking-associated cancer risk to the association between cigarette smoking and first primary smoking-associated cancer risk. With data from 754,855 participants from NIH-AARP, AHS, PLCO and IWHS, Cox proportional hazards regression was used to assess the association between smoking behaviors and first primary smoking-associated cancer risk with age as the time scale, adjusting for sex, race, education, body mass index, cohort, and follow-up time.

Finally, we assessed the cumulative incidence of second primary cancers among survivors of each primary cancer site by prediagnostic smoking status, accounting for death as a competing event.[27] When assessing the associations between risk factors and subsequent cancer diagnoses in cancer survivors, our analyses must allow for mortality as a competing risk. Cigarette smoking is known to be associated with mortality, and deaths preclude second cancer diagnoses from occurring, thus competing deaths may distort the observed associations between smoking and second cancer risk, likely attenuating the estimates. Following common approaches,[28] we estimate the cause-specific[29] HRs and the cumulative risks of subsequent cancers.[27] These two approaches have the advantage of focusing on observable or estimable quantities, and do

not require potentially untestable assumptions about the joint distribution of failure times.[29-31] However, caution is still required for interpretation.

RESULTS

In five prospective cohorts, we identified 2,552 individuals with first primary, incident stage I lung cancer, 6,386 with bladder cancer, 3,179 with kidney cancer and 2,967 with head/neck cancer. Eighty second primary smoking-associated cancers occurred in stage I lung cancer survivors, 385 in bladder cancer survivors, 139 in kidney cancer survivors, and 262 in head/neck cancer survivors (distribution of all second cancer diagnoses presented in Appendix Table A2, online only). Table 1 presents baseline characteristics of cancer survivors with and without a second primary smoking-associated cancer

Table 1. Characteristics of Lung (Stage I), Bladder, Kidney, and Head/Neck Cancer Survivors With and Without Second Smoking-Associated Cancer Diagnoses

	Stage I Lung Cancer*				Bladder Cancer*				Kidney Cancer*				Head/Neck Cancer*			
	No Second Primary Cancer		Second Primary Cancer		No Second Primary Cancer		Second Primary Cancer		No Second Primary Cancer		Second Primary Cancer		No Second Primary Cancer		Second Primary Cancer	
Characteristic	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Total	2,472		80		6,001		385		3,040		139		2,705		262	
Age, years																
< 50	10	0.4	0	0	39	0.7	0	0	58	1.9	0	0	54	2.0	1	0.4
50-54	131	5.3	4	5.0	408	6.8	25	6.5	283	9.3	8	5.8	341	12.6	20	7.6
55-59	523	21.2	19	23.8	1,094	18.2	75	19.5	698	23.0	33	23.7	644	23.8	65	24.8
60-64	776	31.4	22	27.5	1,737	29.0	96	24.9	903	29.7	45	32.4	749	27.7	74	28.2
65-69	821	33.2	28	35.0	2,258	37.6	165	42.9	926	30.5	44	31.7	767	28.4	82	31.3
≥ 70	211	8.5	7	8.8	465	7.8	24	6.2	172	5.7	9	6.5	150	5.6	20	7.6
Sex†																
Male	1,475	59.7	56	70.0	4,973	82.9	331	86.0	2,116	69.6	105	75.5	2,069	76.5	220	84.0
Female	997	40.3	24	30.0	1,028	17.1	54	14.0	924	30.4	34	24.5	636	23.5	42	16.0
Race																
White	2,317	93.7	78	97.5	5,748	95.8	373	96.9	2,796	92.0	132	95.0	2,540	93.9	251	95.8
Nonwhite	153	6.2	2	2.5	249	4.2	12	3.1	244	8.0	7	5.0	163	6.0	11	4.2
Missing	2	0.1	0	0	4	0.1	0	0	0	0	0	0	2	0.1	0	0
Education‡																
≤ High school diploma	947	38.3	26	32.5	1,904	31.7	135	35.1	1,011	33.3	36	25.9	899	33.2	99	37.8
Vocational school/some college	946	38.3	42	52.5	2,080	34.7	155	40.3	1,063	35.0	62	44.6	979	36.2	98	37.4
College graduate/graduate school	519	21.0	10	12.5	1,879	31.3	83	21.6	904	29.7	35	25.2	782	28.9	60	22.9
Missing	60	2.4	2	2.5	138	2.3	12	3.1	62	2.0	6	4.3	45	1.7	5	1.9
Smoking status§																
Never	186	7.5	3	3.8	1,080	18.0	28	7.3	1,029	33.9	19	13.7	542	20.0	18	6.9
Former	1,094	44.3	25	31.3	3,323	55.4	184	47.8	1,371	45.1	71	51.1	1,079	39.9	100	38.2
Current	1,192	48.2	52	65.0	1,598	26.6	173	44.9	640	21.1	49	35.3	1.084	40.1	144	55.0
BMI category§																
< 25	1,015	41.1	32	40.0	1,717	28.6	151	39.2	734	24.1	39	28.1	1,001	37.0	101	38.6
25-29.9	969	39.2	33	41.3	2,863	47.7	147	38.2	1,319	43.4	58	41.7	1,110	41.0	108	41.2
≥ 30.0	411	16.6	13	16.3	1,262	21.0	81	21.0	876	28.8	35	25.2	506	18.7	46	17.6
Missing	77	3.1	2	2.5	159	2.7	6	1.6	111	3.7	7	5.0	88	3.3	7	2.7
Current alcohol use																
No	527	21.3	13	16.3	1,051	17.5	62	16.1	690	22.7	24	17.3	570	21.1	62	23.7
Yes	1,298	52.5	42	52.5	3,827	63.8	268	69.6	1,783	58.7	86	61.9	1,727	63.8	141	53.8
Missing	647	26.2	25	31.3	1,123	18.7	55	14.3	667	21.9	29	20.9	408	15.1	59	22.5
Cohort§																
NIH-AARP	1,276	51.6	32	40.0	3,947	65.8	227	59.0	1,864	61.3	78	56.1	1.673	61.9	142	54.2
AHS	82	3.3	2	2.5	240	4.0	6	1.6	193	6.4	2	1.4	160	5.9	10	3.8
ATBC	320	12.9	17	21.3	527	8.8	83	21.6	244	8.0	23	16.6	331	12.2	51	19.5
IWHS	166	6.7	5	6.3	209	3.5	16	4.2	189	6.2	7	5.0	149	5.5	8	3.1
PLCO	628	25.4	24	30.0	1,078	18.0	53	13.8	550	18.1	29	20.9	392	14.5	51	19.5

NOTE. Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) study only includes current smokers. Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial did not collect information on alcohol use at baseline. Second smoking-associated cancers included: cancers of the oral cavity, oropharynx, nasopharynx, hypopharynx, esophagus (adenocarcinoma and squamous cell carcinoma), stomach, colorectum, liver, pancreas, nasal cavity and paranasal sinuses, larynx, lung, uterine cervix, ovary (mucinous), urinary bladder, kidney (body and pelvis) and ureter, and myeloid leukemia.

Abbreviations: AHS, Agricultural Health Study; BMI, body mass index IWHS, Iowa Women's Health Study; NIH-AARP, National Institutes of Health–AARP Diet and Health Study.

*First primary cancer.

†Statistically significant difference between head/neck cancer survivors with and without a second cancer.

‡Statistically significant difference between bladder and kidney cancer survivors with and without a second cancer.

§Statistically significant difference between lung, bladder, kidney and head/neck cancer survivors with and without a second cancer.

Table 2. Association Between Smoking Status and Cigarettes Smoked per Day and Risk of a Second Primary Smoking-Associated Cancer Among Survivors of Lung (Stage I), Bladder, Kidney, and Head/Neck Cancers

Smoking Status	Stage I Lung Cancer				Bladder Cancer				Kidney Cancer				Head/Neck Cancer			
	Second Cancer				Second Cancer				Second Cancer				Second Cancer			
	No	Yes	HR	95% CI	No	Yes	HR	95% CI	No	Yes	HR	95% CI	No	Yes	HR	95% CI
Never	186	3	1.0	Referent	1,080	28	1.0	Referent	1,029	19	1.0	Referent	542	18	1.0	Referent
Former																
< 20 cig/d	419	6	0.90	0.22 to 3.68	1,523	78	1.84	1.19 to 2.85	752	27	1.90	1.05 to 3.47	511	32	1.60	0.87 to 2.81
≥ 20 cig/d*	674	19	1.69	0.48 to 5.94	1,793	106	2.12	1.38 to 3.26	617	44	4.08	2.30 to 7.25	567	66	2.97	1.74 to 5.07
Current																
< 20 cig/d	482	18	2.58	0.74 to 8.98	623	49	2.81	1.76 to 4.50	243	13	3.44	1.67 to 7.08	408	42	2.89	1.64 to 5.07
≥ 20 cig/d*	389	17	3.26	0.92 to 11.6	448	41	3.67	2.25 to 5.99	152	13	5.33	2.55 to 11.1	345	51	4.45	2.56 to 7.73
P trend†				.002				< .001				< .001				< .001

NOTE. Adjusted for age, sex, race, education, body mass index, cohort, time from baseline to first cancer, and follow-up time. Excludes Alpha-Tocopherol, Beta-Carotene Cancer Prevention study, as this cohort was limited to current smokers.

Abbreviations: cig/d, cigarettes per day; HR, hazard ratio.

*Cigarettes per day was collected as a categorical variable in National Institutes of Health–AARP Diet and Health Study; Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; and Agricultural Health Study. The maximum number of cigarettes smoked per day in the Iowa Women's Health Study was as follows: lung (stage I): 60; bladder: 40; kidney: 40; head and neck: 40.

†*P* trends across joint categories of smoking status and intensity categories were estimated by including the categorical exposure variable in the model as a continuous variable.

diagnosis by first primary site. For each first primary cancer site, survivors who developed a second cancer were more likely to be current smokers at baseline than those that did not. Of note, greater than 50% of all cancer cases occurred in the NIH-AARP cohort, as it was the largest study.

The prevalence of current smoking at baseline was higher among individuals that developed stage I lung (41%), bladder (20%), kidney (15%) and head/neck cancers (33%), compared with all cohort participants in NIH-AARP, AHS, PLCO and IWHS (13%). Across all first primary cancer sites, there was a significant trend of increasing risk of second smoking-associated cancers across categories of prediagnostic smoking status and cigarettes smoked per day (Table 2). Compared with never-smokers, current smoking status with ≥ 20 cigarettes per day was associated with an increased risk of second smoking-associated cancer among survivors of stage I lung cancer (HR = 3.26; 95% CI, 0.92 to 11.6), bladder cancer (HR = 3.67; 95% CI, 2.21 to 5.99), head/neck cancer (HR = 4.45; 95% CI, 2.56 to 7.73), and kidney cancer (HR = 5.33; 95% CI, 2.55 to 11.1), with apparently stronger risk estimates in the pooled population restricted to 3-year survivors (Appendix Table A3, online only). Study-specific estimates were generally underpowered and are presented in Appendix Table A4 (online only). No significant interactions were observed between smoking and cohort (all *P* interactions > 0.4). Associations between cigarette smoking and first smoking-associated cancer risk were similar to associations observed for second smoking-associated cancer risk among cancer survivors. Compared with never-smokers, current smokers who smoked ≥ 20 cigarettes per day had a 5.4-fold increased risk of any first primary smoking-associated cancer. The HRs for current smokers who smoked less than 20 cigarettes per day (HR = 3.72), former smokers who smoked ≥ 20 cigarettes per day (HR = 2.35) and former smokers who smoked less than 20 cigarettes per day (HR = 1.49) were also elevated (Appendix Table A5, online only).

Among current smokers at baseline, the risk of second primary smoking-associated cancers increased significantly with increasing smoking intensity and among ever smokers at baseline, risk increased significantly with increasing pack-years smoked for survivors of kidney (*P* trend = .02 and .005, respectively) and head/neck cancers (*P* trend = .008 and .02, respectively). In contrast, no significant trend in smoking-associated cancer risk was observed across categories of cigarettes per day or pack-years smoked for survivors of stage I lung (*P* trend = .97 and .58, respectively) and bladder cancers (*P* trend = .45 and .07, respectively; Figs 1 and 2). Among former smokers at baseline, time since quitting was significantly inversely associated with increased second smoking-associated cancer risk for survivors of bladder (*P* trend <

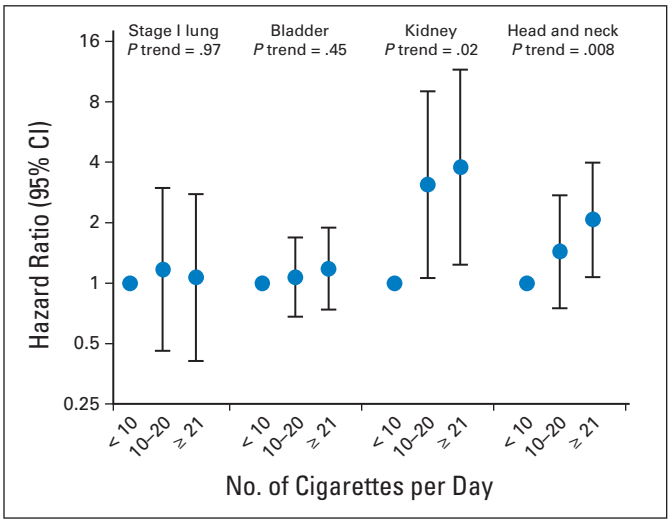

Fig 1. Association between cigarettes smoked per day at baseline and subsequent risk of second smoking-associated cancers among current smokers with stage I lung, bladder, kidney, and head/neck cancers. Points represent odds ratios and lines represent 95% CIs. Cigarettes per day was collected as a categorical variable in the National Institutes of Health–AARP Diet and Health Study, the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial, and the Agricultural Health Study. The maximum number of cigarettes smoked per day among current smokers in the Iowa Women's Health Study was as follows: lung (stage I): 50; bladder: 40; kidney: 25; head and neck: 40, and in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study was as follows: lung (stage I): 60; bladder: 60; kidney: 55; head and neck: 60.

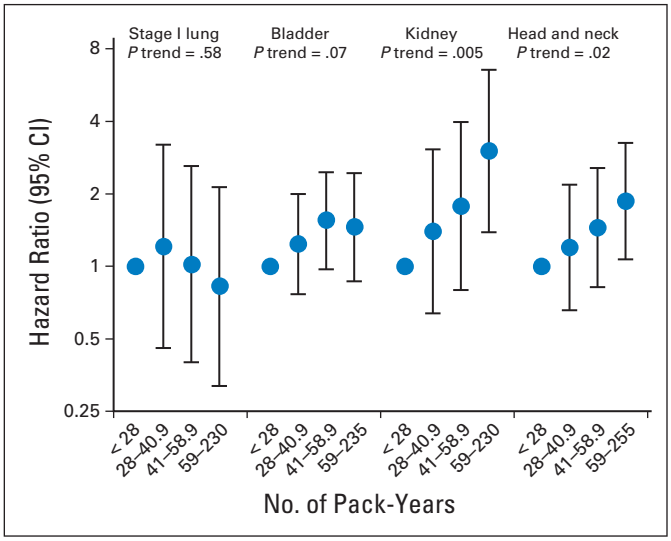

Fig 2. Association between pack-years smoked at baseline and subsequent risk of second smoking-associated cancers among current smokers with stage I lung, bladder, kidney, and head/neck cancers. Points represent odds ratios and lines represent 95% CIs.

.001), kidney (P trend = .002) and head/neck cancers (P trend < .001), but not stage I lung cancers (P trend = .99; Fig 3).

When anatomic sub-sites within head/neck cancers were examined, the strongest associations between current smokers with ≥ 20 cigarettes per day and second smoking-associated cancer risk were observed among survivors of oral cavity (HR = 6.29; 95% CI, 2.10 to 18.8) and laryngeal cancers (HR = 8.20; 95% CI, 1.89 to 35.6; Appendix Table A6, online only).

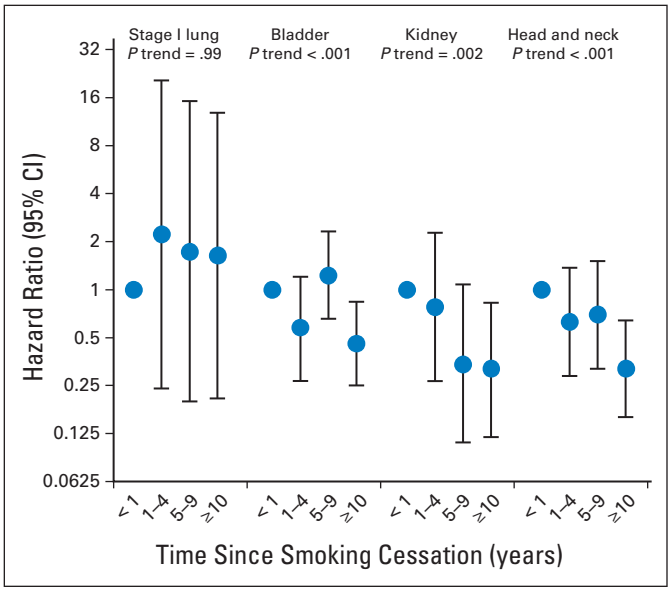

Fig 3. Association between years since smoking cessation at baseline and subsequent risk of second smoking-associated cancers among former smokers with stage I lung, bladder, kidney, and head/neck cancers. Points represent odds ratios and lines represent 95% CIs. Years since smoking cessation was collected as a categorical variable in the National Institutes of Health–AARP Diet and Health Study. The maximum number of years since smoking cessation in the Iowa Women's Health Study was as follows: lung (stage I): 32; bladder: 41; kidney: 36; head and neck: 40, and in the Prostate, Lung, Colorectal and Ovarian Screening Trial was as follows: lung (stage I): 41; bladder: 58; kidney: 53; head and neck: 53.

Prediagnostic smoking was significantly associated with mortality in each survivor cohort (Table 3). Compared with never-smokers, current smokers who smoked ≥ 20 cigarettes per day had an increased risk of death among survivors of stage I lung (HR = 3.08; 95% CI, 2.18 to 4.33), bladder (HR = 2.48; 95% CI, 1.99 to 3.09), kidney (HR = 1.57; 95% CI, 1.18 to 2.08), and head/neck cancers (HR = 1.68; 95% CI, 1.34 to 2.10). Appendix Figure A1 (online only) presents the absolute risk of death and second smoking-associated cancers in each survivor cohort by prediagnostic smoking status. These figures emphasize the importance of death as a competing risk in survivors of stage I lung, bladder, kidney and head/neck cancers. For example, the 5-year cumulative incidence of death was higher among baseline current smokers compared with never-smokers among survivors of stage I lung cancer (51.2% *v* 25.0%), bladder cancer (26.0% *v* 15.5%), kidney cancer (42.2% *v* 31.7%) and head/neck cancer (38.4% *v* 30.0%).

DISCUSSION

In the largest study to date, with observational data for over 15,000 cancer survivors from five prospective cohorts, we showed that cigarette smoking before first cancer diagnosis is associated with subsequent smoking-associated cancer risk among survivors of stage I lung, bladder, kidney, and head/neck cancers. Risks decreased with a greater number of years since smoking cessation in former smoking survivors of bladder, kidney, and head/neck cancers, and were similar to those observed for first primary smoking-associated cancers.

In the United States, 44% of malignancies occurring among survivors of an alcohol or tobacco-related cancer are also alcohol or tobacco-related cancers.[7] Prior analyses based on large registries conjectured that the increased rate of second primary smoking-associated cancers following first primary smoking-associated cancers was due to smoking as a shared risk factor; however, those studies were unable to directly address this question. Our results are consistent with previous generally smaller studies among survivors of lung or head/neck cancers.[8-12,14,15] In addition, we provide novel data that prediagnostic smoking increases risk of second smoking-associated cancers in survivors of bladder and kidney cancers. Further, we have shown that the strength of the association between smoking and second smoking-associated cancer risk does not exceed that of smoking and first smoking-associated cancer risk. This may indicate that the increased risk of smoking-associated cancers among survivors of smoking-associated cancers is due to increased smoking prevalence in this group of cancer survivors (15% to 41% *v* 13%), though we could not rule out a role for increased susceptibility to smoking-related damage.

In addition, we have shown that the pooling of large cohort studies with available risk behavioral information is essential to address questions regarding second cancer risk. The main strength of our analysis is the pooling of five large, well-established cohort studies with demographic and behavioral information and extensive follow-up. Studying second cancer risk requires a large number of cancer survivors, and the association between smoking and second cancer risk could not have been addressed in any of these studies alone (Appendix Table A2). However, our approach also had several limitations that reflect general challenges in studying second cancers in existing cohorts, which have been explored by our group in detail previously.[21]

Table 3. Association Between Smoking Status and Death Among Survivors of First Primary Lung (stage I), Bladder, Kidney, and Head/Neck Cancers

Smoking Status	Stage I Lung Cancer				Bladder Cancer				Kidney Cancer				Head/Neck Cancer			
	Second Cancer				Second Cancer				Second Cancer				Second Cancer			
	No	Yes	HR	95% CI	No	Yes	HR	95% CI	No	Yes	HR	95% CI	No	Yes	HR	95% CI
Never	147	42	1.00	Referent	899	209	1.00	Referent	723	325	1.00	Referent	381	179	1.00	Referent
Former																
< 20 cig/d	261	164	1.87	1.32 to 2.64	1,279	322	1.23	1.03 to 1.48	534	245	1.08	0.91 to 1.28	382	161	0.95	0.77 to 1.19
≥ 20 cig/d*	382	311	2.22	1.59 to 3.10	1,449	450	1.57	1.31 to 1.87	444	217	1.21	1.01 to 1.46	419	214	1.19	0.96 to 1.47
Current																
< 20 cig/d	261	239	2.38	1.70 to 3.32	488	184	1.71	1.40 to 2.10	144	112	1.57	1.26 to 1.96	243	207	1.64	1.32 to 2.02
≥ 20 cig/d*	197	209	3.08	2.18 to 4.33	337	152	2.48	1.99 to 3.09	103	62	1.57	1.18 to 2.08	227	169	1.68	1.34 to 2.10
P trend†				< .001				< .001				< .001				< .001

NOTE. Adjusted for age, sex, race, education, body mass index, cohort, time from baseline to first cancer, and follow-up time. Excludes Alpha-Tocopherol, Beta-Carotene Cancer Prevention study, as this cohort was limited to current smokers.

Abbreviations: cig/d, cigarettes per day; HR, hazard ratio.

*Cigarettes per day was collected as a categorical variable in National Institutes of Health–AARP Diet and Health Study; Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; and Agricultural Health Study. The maximum number of cigarettes smoked per day in the Iowa Women's Health Study was as follows: lung (stage I): 60; bladder: 40; kidney: 40; head and neck: 40.

†*P* trends across joint categories of smoking status and intensity categories were estimated by including the categorical exposure variable in the model as a continuous variable.

First, our analysis lacked treatment data, as the participating cohorts do not collect treatment information on cancer cases. Further, despite the over 15,000 cancer survivors included in this study, our power was limited based on a relatively small number of second cancers. In addition, our estimates relied on baseline, prediagnostic assessments of smoking behaviors, as questionnaires in each study were not administered regularly enough to ascertain smoking status at the time of diagnosis with a first cancer, the ideal time point for assessing associations with cancer risk. In addition, among current smokers at baseline, less than 25% had follow-up questionnaires administered after their initial cancer diagnosis, prohibiting the evaluation of change in smoking status after cancer diagnosis and subsequent risk. Further, our reliance on baseline questionnaire data (collected at varying times before first cancer diagnosis) may have resulted in more misclassification of exposure for the assessment of second cancer risk than first cancer risk. As a result, current smokers at baseline who subsequently quit would be included in the estimates for current smokers, potentially attenuating the results. To improve our assessment of smoking and second cancer risk, collaboration of additional cohorts with more frequently administered questionnaires is needed.

When assessing associations between risk factors and subsequent cancer diagnoses in cancer survivors, it is important to consider the impact of mortality. As cigarette smoking is associated with additional diverse causes of mortality, and deaths preclude second cancer diagnoses from occurring, competing deaths may distort the observed associations between smoking and second cancer risk. This is evidenced in our analysis restricted to 3-year survivors, which showed stronger associations between cigarette smoking and second cancer risk, and in our attenuated results for lung cancer survivors, who have the poorest prognosis of the survivor cohorts. Due to the competing risk of death, we have shown the cause-specific HR, which presents the association between smoking and second cancer risk in the presence of competing mortality. To highlight the importance of competing events in this analysis, we have also shown the association between cigarette smoking and death, as well as the absolute risk of mortality and second cancers, taking competing deaths into account. The strong associations between cigarette smoking and death reinforce the need for smoking cessation among cancer survivors.

In addition to increasing the risk of mortality and subsequent malignancies, cigarette smoking among cancer patients also increases surgical complications and toxicity from treatment with chemotherapy and radiation.[32,33] The American Society for Clinical Oncology (ASCO) therefore advocates for the integration of tobacco cessation into clinical care.[32] However, a recent survey of ASCO members found that only 58% of providers always advise their patients to quit smoking and only 39% usually provide treatment or refer patients for treatment for tobacco dependence.[34]

As the population of cancer survivors continues to grow, understanding risk factors for second cancers in this population is crucial. Cigarette smoking remains common in cancer survivors, even among those diagnosed with tobacco-related cancer.[3-6] Cancer patients may not realize that they are at a higher risk of treatment complications, second primary cancers and death if they continue to smoke. Though more research is needed on smoking and second cancer risks, health care providers should emphasize the importance of smoking cessation to cancer patients.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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GLOSSARY TERMS

cumulative risk: a measure of risk of an event (usually disease occurrence) during a specified time period.

Surveillance, Epidemiology, and End Results (SEER): a national cancer registry that collects information from all incident malignancies in multiple geographic areas of the United States.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Cigarette Smoking Prior to First Cancer and Risk of Second Smoking-Associated Cancers Among Survivors of Bladder, Kidney, Head and Neck, and Stage I Lung Cancers

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Appendix

Table A1. Association Between Smoking Status and Cigarettes Smoked per Day and Risk of a Second Primary Smoking-Associated Cancer Among Survivors of Lung (stage I), Bladder, Kidney, and Head/Neck Cancers, Including Follow-Up Time and Event Occurring Within 30 Days of Diagnosis

Smoking Status	Stage I Lung		Bladder		Kidney		Head/Neck Cancer	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Never	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
Former								
< 20 cig/d	0.56	0.17 to 1.88	1.94	1.25 to 2.99	1.95	1.11 to 3.42	1.63	0.91 to 2.91
≥ 20 cig/d*	1.09	0.39 to 3.05	2.22	1.45 to 3.40	3.86	2.24 to 6.65	3.08	1.81 to 5.25
Current								
< 20 cig/d	2.05	0.75 to 5.89	2.12	1.96 to 4.95	3.45	1.75 to 6.78	2.90	1.65 to 5.09
≥ 20 cig/d*	2.08	0.73 to 5.59	4.10	2.54 to 6.62	5.01	2.49 to 10.1	4.84	2.80 to 8.36
P trend†	.04		< .001		.001		< .001	

NOTE. Adjusted for age, sex, race, education, body mass index, cohort, time from baseline to first cancer, and follow-up time. Excludes Alpha-Tocopherol, Beta-Carotene Cancer Prevention study, given that this cohort was limited to current smokers.

Abbreviations: cig/d, cigarettes per day; HR, hazard ratio.

*Cigarettes per day was collected as a categorical variable in National Institutes of Health–AARP Diet and Health Study; Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; and Agricultural Health Study. The maximum number of cigarettes smoked per day in the Iowa Women's Health Study was as follows: lung (stage I): 60; bladder: 40; kidney: 40; head and neck: 40.

†*P* trends across joint categories of smoking status and intensity categories were estimated by including the categorical exposure variable in the model as a continuous variable.

Table A2. Second Cancer Types After a Primary Cancer Diagnosis of Stage I Lung Cancer, Bladder Cancer, Kidney Cancer, and Head/Neck Cancer

Location	Stage I Lung Cancer	Bladder Cancer	Kidney Cancer	Head/Neck Cancer
Lip	1	2	0	**0**
Tongue	0	2	0	**11**
Salivary gland	1	2	0	**4**
Floor of mouth	2	2	1	**4**
Gum and other mouth	0	1	0	**14**
Nasopharynx	1	0	0	**1**
Tonsil	1	1	0	**6**
Oropharynx	0	1	0	**4**
Hypopharynx	2	1	0	**5**
Other oral cavity and pharynx	1	0	0	**3**
Esophagus	4	7	2	14
Stomach	4	14	6	5
Small intestine	1	3	2	1
Cecum	8	6	5	7
Appendix	0	0	1	0
Ascending colon	2	13	5	3
Hepatic flexure	0	6	2	0
Transverse colon	0	0	2	2
Splenic flexure	2	1	0	1
Descending colon	0	3	2	0
Sigmoid colon	2	17	5	9
Large intestine, NOS	0	3	1	1
Rectosigmoid junction	0	3	0	4
Rectum	1	17	1	6
Anus, anal canal, and anorectum	0	0	0	3
Liver	3	9	2	7
Intrahepatic bile duct	0	1	1	0
Gallbladder	0	2	1	0
Other biliary	0	1	0	1
Pancreas	11	19	9	14
Nose, nasal cavity, and middle ear	0	1	0	0
Peritoneum, omentum, and mesentery	0	0	1	0
Other digestive organs	0	0	0	1
Larynx	7	11	3	5
Lung and bronchus	**74**	198	57	153
Trachea, mediastinum, and other respiratory organs	1	0	0	3
Bones and joints	0	0	1	0
Soft tissue including heart	1	2	2	0
Melanoma	6	37	15	12
Other nonepithelial skin	0	0	0	1
Breast	19	22	24	15
Cervix	0	0	1	1
Corpus uteri	1	3	2	0
Ovary	2	3	0	3
Vagina	1	1	0	0
Vulva	0	1	0	1
Prostate	61	365	101	70
Testis	0	1	0	0
Ureter	0	2	0	1
Urinary bladder	10	**13**	31	23
Kidney and renal pelvis	14	33	**22**	10
Other urinary organs	0	3	1	2
Eye and orbit	1	3	2	0
Brain	1	3	3	2
Cranial nerves, other nervous system	0	0	1	0
Thyroid	2	7	7	4
Hodgkin nodal	0	1	2	0
NHL nodal	11	23	6	8
Extranodal	5	6	1	2
Myeloma	1	6	8	3

(continued on following page)

Table A2. Second Cancer Types After a Primary Cancer Diagnosis of Stage I Lung Cancer, Bladder Cancer, Kidney Cancer, and Head/Neck Cancer (continued)

Location	Stage I Lung Cancer	Bladder Cancer	Kidney Cancer	Head/Neck Cancer
Chronic lymphocytic leukemia	3	9	2	3
Acute myeloid leukemia	2	10	2	4
Chronic myeloid leukemia	1	2	1	0
Acute monocytic leukemia	0	1	0	0
Aleukemic, subleukemic NOS	0	0	0	1
Mesothelioma	1	4	1	1
Miscellaneous	4	26	5	8
Invalid	1	5	2	3

NOTE. Bold indicates same-site multiple primaries that were censored in each site-specific analysis.
Abbreviations: NHL, non-Hodgkin lymphoma; NOS, not otherwise specified.

Table A3. Association Between Smoking Status and Risk of a Second Primary Smoking-Associated Cancer Among 3-Year Survivors Of Lung (stage I), Bladder, Kidney, and Head/Neck Cancers

Smoking Status	Stage I Lung Cancer				Bladder Cancer				Kidney Cancer				Head/Neck Cancer			
	Second Cancer				Second Cancer				Second Cancer				Second Cancer			
	No	Yes	HR	95% CI	No	Yes	HR	95% CI	No	Yes	HR	95% CI	No	Yes	HR	95% CI
Never	101	1	1.00	Referent	606	12	1.00	Referent	516	5	1.00	Referent	305	4	1.00	Referent
Former																
< 20 cig/d	213	3	1.52	0.15 to 15.0	826	32	1.76	0.90 to 3.44	360	10	2.32	0.77 to 6.97	287	18	3.74	1.25 to 11.1
≥ 20 cig/d*	309	7	2.59	0.30 to 22.4	976	43	2.05	1.06 to 3.95	262	16	5.51	1.92 to 15.8	290	26	5.12	1.76 to 14.9
Current																
< 20 cig/d	247	6	2.87	0.34 to 24.4	340	25	3.11	1.55 to 6.25	99	7	5.80	1.80 to 18.7	209	25	7.23	2.49 to 21.0
≥ 20 cig/d*	175	6	6.02	0.67 to 54.0	238	19	3.95	1.89 to 8.27	64	5	6.61	1.81 to 24.1	148	23	9.25	3.15 to 27.2
P trend†				.04				< .001				.001				< .001

NOTE. Adjusted for age, sex, race, education, body mass index, cohort, time from baseline to first cancer, and follow-up time. Excludes Alpha-Tocopherol, Beta-Carotene Cancer Prevention study, given that this cohort was limited to current smokers.
Abbreviations: cig/d, cigarettes per day; HR, hazard ratio.
*Cigarettes per day was collected as a categorical variable in National Institutes of Health–AARP Diet and Health Study; Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; and Agricultural Health Study. The maximum number of cigarettes smoked per day in the Iowa Women's Health Study was as follows: lung (stage I): 60; bladder: 40; kidney: 40; head and neck: 40.
†*P* trends across joint categories of smoking status and intensity categories were estimated by including the categorical exposure variable in the model as a continuous variable.

Table A4. Association Between Smoking Status and Risk of a Second Primary Smoking-Associated Cancer Among Survivors of Lung, Bladder, Kidney, and Head/Neck Cancers

First Primary Cancer	Cohort	Smoking Status	No Second Cancer	Second Cancer	HR	95% CI
Stage I Lung	NIH-AARP	Never	77	0	1.00	
		Former	698	16	> 1,000	—
		Current	501	16	> 1,000	—
	AHS	Never	19	0	1.00	
		Former	29	1	19.85	—
		Current	34	1	0.23	—
	IWHS	Never	29	1	1.00	
		Former	42	0	0.00	—
		Current	95	4	1.46	0.08 to 27.54
	PLCO	Never	61	2	1.00	
		Former	325	8	0.48	0.09 to 2.49
		Current	242	14	1.31	0.26 to 6.58
Bladder	NIH-AARP	Never	656	14	1.00	
		Former	2,529	153	2.64	1.52 to 4.59
		Current	762	60	3.63	2.02 to 6.52
	AHS	Never	73	2	1.00	
		Former	113	2	0.52	0.06 to 4.84
		Current	54	2	0.64	0.07 to 6.19
	IWHS	Never	101	6	1.00	
		Former	52	1	0.32	0.04 to 2.73
		Current	56	9	2.36	0.73 to 7.63
	PLCO	Never	250	6	1.00	
		Former	629	28	1.77	0.72 to 4.36
		Current	199	19	4.53	1.74 to 11.8
Kidney	NIH-AARP	Never	579	12	1.00	
		Former	1,011	47	2.23	1.17 to 4.25
		Current	274	19	3.74	1.79 to 7.79
	AHS	Never	92	0	1.00	
		Former	69	2	—	—
		Current	32	0	—	—
	IWHS	Never	126	4	1.00	
		Former	39	1	1.12	0.10 to 12.7
		Current	24	2	7.74	0.76 to 78.8
	PLCO	Never	232	3	1.00	
		Former	252	21	5.45	1.56 to 19.05
		Current	66	5	5.77	1.29 to 25.85
Head/neck	NIH-AARP	Never	319	10	1.00	
		Former	814	67	2.43	1.24 to 4.76
		Current	540	65	3.97	2.02 to 7.82
	AHS	Never	63	1	1.00	
		Former	46	5	1.37	0.10 to 18.6
		Current	51	4	1.78	0.13 to 25.2
	IWHS	Never	82	3	1.00	
		Former	30	1	2.23	0.37 to 13.5
		Current	37	4	1.24	0.11 to 14.3
	PLCO	Never	78	4	1.00	
		Former	189	27	2.39	0.81 to 7.05
		Current	125	20	3.66	1.18 to 11.3

NOTE. Adjusted for age, sex, race, education, body mass index, cohort, time from baseline to first cancer, and follow-up time. Excludes Alpha-Tocopherol, Beta-Carotene Cancer Prevention study, as this cohort was limited to current smokers.

Abbreviations: AHS, Agricultural Health Study; HR, hazard ratio, IWHS, Iowa Women's Health Study; NIH-AARP, National Institutes of Health-AARP Diet and Health Study; PLCO, Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial.

Table A5. Association Between Smoking Status and Risk of a First Primary Smoking-Associated Cancer

Smoking Status	Cancer Case		HR	95% CI
	No	Yes		
Never	307,651	11,052	1.00	Referent
Former				
< 20 cig/d	190,400	11,025	1.49	1.45 to 1.53
≥ 20 cig/d	126,965	12,175	2.35	2.29 to 2.42
Current				
< 20 cig/d	54,956	6,859	3.72	3.60 to 3.83
≥ 20 cig/d	27,797	4,957	5.41	5.22 to 5.60
P trend*				< .001

NOTE. Adjusted for age, sex, race, education, body mass index, cohort, time from baseline to first cancer, and follow-up time. Excludes Alpha-Tocopherol, Beta-Carotene Cancer Prevention study, as this cohort was limited to current smokers.
Abbreviations: cig/d, cigarettes per day; HR, hazard ratio.
**P* trends across joint categories of smoking status and intensity categories were estimated by including the categorical exposure variable in the model as a continuous variable.

Table A6. Association Between Smoking Status and Risk of a Second Primary Smoking-Associated Cancer Among Survivors of Head/Neck Cancer, by Site

Smoking Status	Oral Cavity				Oropharynx				Other Head/Neck				Larynx			
	Second Cancer				Second Cancer				Second Cancer				Second Cancer			
	No	Yes	HR	95% CI	No	Yes	HR	95% CI	No	Yes	HR	95% CI	No	Yes	HR	95% CI
Never	198	5	1.00	Referent	123	4	1.00	Referent	149	7	1.00	Referent	72	2	1.00	Referent
Former																
< 20 cig/d	143	8	1.92	0.62 to 5.98	108	7	1.31	0.37 to 4.64	106	8	1.84	0.62 to 5.46	154	9	1.92	0.41 to 8.94
≥ 20 cig/d*	122	15	3.58	1.22 to 10.5	152	11	1.29	0.40 to 4.16	120	7	1.34	0.42 to 4.28	173	33	7.20	1.72 to 30.2
Current																
< 20 cig/d	81	14	5.22	1.78 to 15.3	85	6	2.81	0.74 to 10.6	83	6	1.47	0.44 to 4.94	159	16	4.06	0.92 to 17.9
≥ 20 cig/d*	61	12	6.29	2.10 to 18.8	84	6	2.38	0.65 to 8.73	58	9	3.59	1.12 to 11.5	142	24	8.20	1.89 to 35.6
P trend†				< .001				.09				.09				< .001

NOTE. Adjusted for age, sex, race, education, body mass index, cohort, time from baseline to first cancer, and follow-up time. Excludes Alpha-Tocopherol, Beta-Carotene Cancer Prevention study, as this cohort was limited to current smokers.
Abbreviations: cig/d, cigarettes per day; HR, hazard ratio.
**Cigarettes per day was collected as a categorical variable in National Institutes of Health–AARP Diet and Health Study; Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; and Agricultural Health Study. The maximum number of cigarettes smoked per day in the Iowa Women's Health Study was as follows: lung (stage I): 60; bladder: 40; kidney: 40; head and neck: 40.*
†P trends across joint categories of smoking status and intensity categories were estimated by including the categorical exposure variable in the model as a continuous variable.

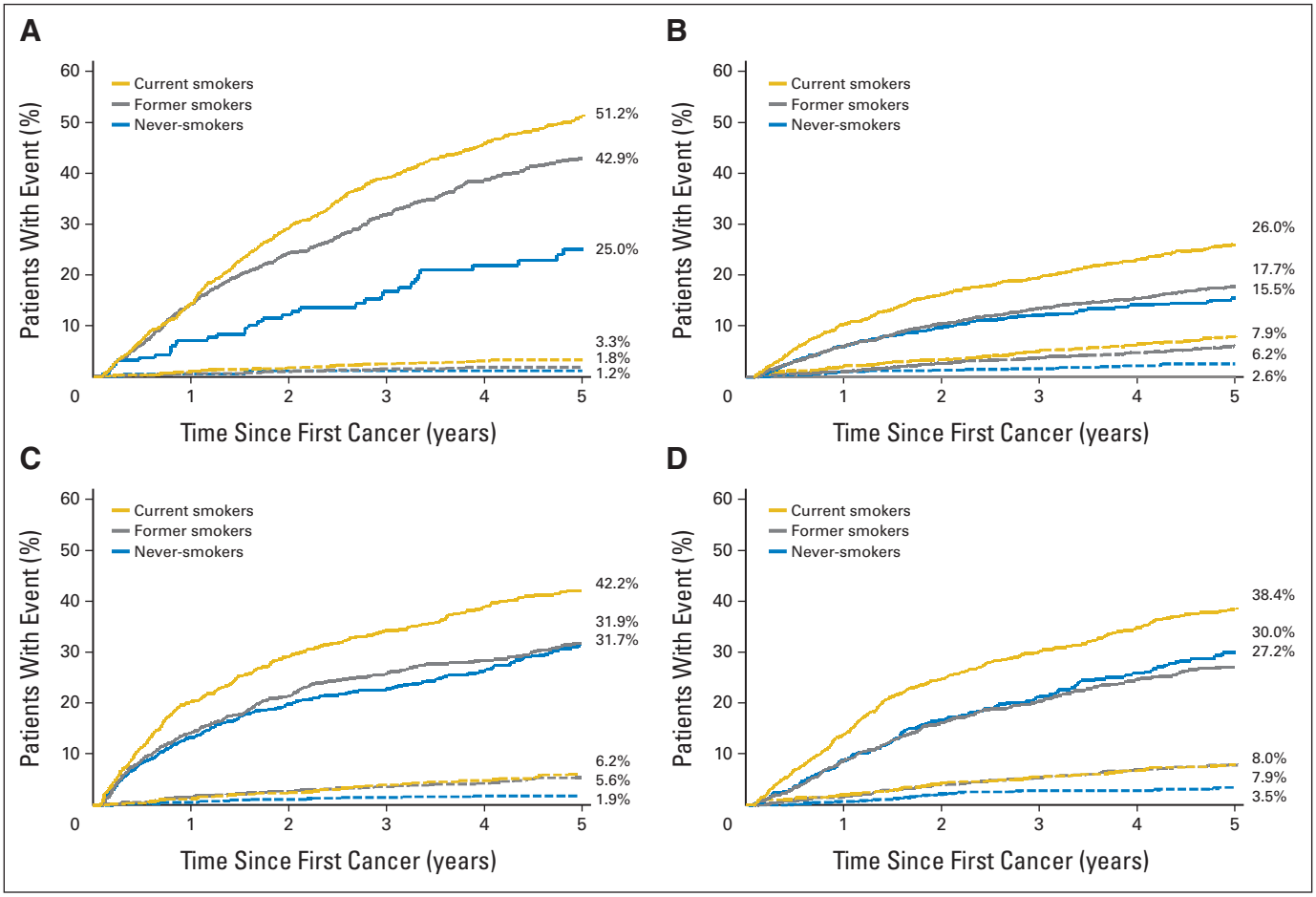

Fig A1. Five-year cumulative incidence of second smoking-associated malignancies and death among survivors of first primary (A) stage I lung, (B) bladder, (C) kidney, and (D) head/neck cancers. Gold lines represent current smokers, gray lines represent former smokers, and blue lines represent never-smokers. Solid lines indicate 5-year cumulative incidence of death and dashed lines indicate 5-year cumulative incidence of smoking-associated second cancers.