Research Article

Cancer Epidemiology, Biomarkers & Prevention

Tobacco Use and Cancer Risk in the Agricultural Health Study

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Abstract

Background: Cigarettes are well known to cause cancer, but less is known about the risks of other tobacco products and use of more than one product.

Methods: We examined cancer incidence in relation to exclusive use of six tobacco products [cigarettes, other combustibles (pipe, cigar, cigarillo), and smokeless tobacco (chewing tobacco, snuff)] in the Agricultural Health Study. We also examined the added cancer risks associated with use of cigarettes and other tobacco products.

Results: In our study population of 84,015, ever use of smokeless tobacco was higher than the general United States population, whereas cigarette use was lower and other combustible product use was about the same. The strongest associations for exclusive ever use were for lung cancer [cigarettes HR = 15.48; 95% confidence interval (CI), 11.95–20.06; other combustible tobacco HR = 3.44; 95% CI, 1.53–7.71; smokeless tobacco HR = 2.21; 95% CI, 1.11–4.42]. Compared with exclusive cigarette smokers, cigarette smokers who additionally ever-used another combustible product had higher risks of smoking-related cancers (HR = 1.16; 95% CI, 1.04–1.30), especially among those who smoked cigarettes for more than 15 years.

Conclusions and Impact: Cigarette smokers who additionally ever used smokeless tobacco had cancer risks similar to exclusive cigarette smokers. Users of cigarettes and other combustible tobacco may have higher risks of certain cancers than exclusive cigarette users. *Cancer Epidemiol Biomarkers Prev; 26(5); 769–78. ©2016 AACR.*

Introduction

Cigarettes are the most common type of tobacco used in the United States, followed by non-cigarette–combustible products (e.g., pipe, cigar, cigarillo) and smokeless tobacco (e.g., chewing, snuff, snus; refs. 1, 2). However, there is some variation in tobacco use by geographical region (1–3). For example, use of smokeless tobacco among U.S. adults is more than twice as common in rural and agricultural populations compared with urban populations (3). Furthermore, use of more than one tobacco product, either at the same time or sequentially, has been estimated to constitute a considerable proportion of tobacco users (4). For example, based on a 2008 nationally representative survey, approximately 40% of smokeless tobacco users reported also smoking cigarettes (4).

Tobacco is one of the leading causes of cancer, accounting for approximately 16% of all cancer diagnoses and 30% of all cancer deaths in the United States (5–7). In 2009, the International Agency for Research on Cancer (IARC) reassessed the carcinogenicity of combustible and smokeless tobacco. They found sufficient evidence linking cigarettes and non-cigarette–combustible products with oropharyngeal, stomach, colorectal, liver, pancreas, nasal cavity, lung, cervix, ovary, bladder, kidney, ureter, and myeloid leukemia (8). They also reported sufficient evidence linking smokeless tobacco with cancer of the oral cavity, esophagus, and pancreas, but did not have sufficient evidence for lung cancer (8). Despite this determination, less is known about the cancer risks associated with individual non-cigarette–combustible and smokeless tobacco products, as well the risks associated with more than one type of tobacco product.

In this study, we examine the risks of cancer associated with exclusive use of cigarettes, pipes, cigars, cigarillos, chewing tobacco, and snuff, as well as the use of cigarettes and at least one additional tobacco product. This analysis is conducted within the Agricultural Health Study (AHS), a prospective cohort of participants recruited in Iowa and North Carolina (9). Previous studies in the AHS cohort have reported lower risks of lung cancer compared with the general U.S. population, which has been attributed partially to the lower prevalence of cigarette smoking compared with the general U.S. population (10, 11). This is the first study to evaluate the use of cigarettes, other combustible tobacco and smokeless tobacco, and cancer risk in the AHS cohort.

Materials and Methods

The AHS is a prospective cohort study of 89,655 participants, including licensed private pesticide applicators and their spouses recruited in Iowa and North Carolina, as well as commercial pesticide applicators recruited in Iowa. Participants were enrolled

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Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

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between 1993 and 1997; 82% of applicators seeking pesticide licensing and an estimated 75% of spouses of private applicators chose to participate in the study. A more detailed description of the study and the population has been previously published (9).

Cancer cases were identified using population-based state cancer registries. Incident cancer cases diagnosed between enrolment and 2010 in North Carolina and 2011 in Iowa were included. Tobacco use, as well as demographic, lifestyle, and occupational data were ascertained by self-completed questionnaire. Participants were considered to be former smokers if they reported using at least 100 cigarettes during their lifetime but were not smoking at enrolment. Participants were considered current smokers if they reported using at least 100 cigarettes during their lifetime and were smoking at enrolment. Former and current smokers reported cigarette smoking duration and number of cigarettes smoked per day, which we used to calculate pack-years. For tobacco products other than cigarettes, participants were asked whether they used pipes, cigars, cigarillos, chewing tobacco, or snuff on a regular basis for 6 months or longer. Information on status (former, current), frequency, and duration of use was not collected for non-cigarette tobacco products.

Statistical analysis

Our analysis included 84,015 AHS participants who were cancer free at enrolment and had complete information on cigarette smoking use. We excluded 3,730 participants with missing information on cigarette smoking and 1,911 with prevalent cancers at enrolment. We calculated the prevalence of ever using any tobacco, which was based on use of cigarettes, pipes, cigars, cigarillos, chewing tobacco, or snuff. We also calculated the prevalence of ever using each of these products, using only one of these products (exclusive product use), as well as using cigarettes and at least one additional product (dual product use). In this article, we refer to dual tobacco users as persons who ever smoked cigarettes (former or current) and ever users of another type of tobacco product.

Potential confounding factors for each cancer site evaluated were identified on the basis of a review of the literature. We compared tobacco and non-tobacco users by gender, age at enrolment (<30, 30–39, 40–49, 50–59, 60–69, 70+), state of residence (IA, NC), race (white, black, other), education (less than high school, high school or more, other), BMI (<18.5, 18.5–24.9, 25–29.9, 30+ kg/m^2), alcohol consumption in the year prior to enrolment (never, ever), usual number of alcoholic drinks in the year prior to enrolment (none, $\leq$3 per month, 1–4 per week, $\geq$5 per week), and fruit and vegetable intake in the year prior to enrolment (<1, 1–2, $\geq$3 servings per day). We also examined the distribution of these characteristics among exclusive and dual product users, and between participants with and without cancer. We computed average cigarettes per day, years smoked, and cigarette pack-years adjusted for age, gender, race, state of residence, education, and alcohol frequency for exclusive and dual product users.

We examined associations of exclusive and dual product use with total cancer and tobacco-related cancer incidence. Tobacco-related cancers included bladder, colon, cervix, esophagus, kidney, larynx, lip, liver, lung, myeloid leukemia, nasal and sinus, oral cavity, pancreas, pharynx, rectum, stomach, tongue, ureter, and uterus (5, 6, 8). Because of the small number of exposed cases for some cancer sites, we evaluated the following sites in groups: gastrointestinal (colon, esophagus, liver, pancreas, rectum, stomach), urinary (bladder, kidney, ureter), and head and neck (larynx, lip, nasal and sinus, oral cavity, pharynx, tongue). HR and 95% confidence intervals (95% CI) for cancer incidence were calculated using Cox proportional hazards regression models with person-years participating in the study as the time-dependent variable. Person-years were censored at the earliest of the following: cancer diagnosis, death, movement out of state, or end of follow-up (December 31, 2010 or 2011, in NC or IA, respectively). Models were adjusted for age, gender, race, state of residence, education, alcohol frequency, cigarettes per days, and years smoked cigarettes. As this is an agricultural cohort, we evaluated the potential impact of pesticide use on outcomes by further adjusting for individual pesticides that have been previously found to be associated with cancer in the AHS. Because of differences in usage patterns, we also examined cancer risk stratified by gender, state of residence, and cigarette smoking status, duration, and frequency. HRs based on fewer than four exposed cases were not reported. SAS version 9.1 and the AHS data release P1REL201209 were used to conduct all analyses.

Novelty and impact

In the AHS, the prevalence of smokeless tobacco use is higher than the general U.S. population, but the prevalence of cigarette use is lower. Therefore, this is one of the few studies with sufficient statistical power to evaluate cancer incidence in relation to exclusive and dual use of multiple types of tobacco products.

Results

Of the 84,015 study participants, 38,810 (46.2%) reported ever using at least one of the six tobacco products we evaluated. Fifty-six percent of the 53,071 male participants and 29% of the 30,944 female participants ever used tobacco. Fifty-eight percent of the 28,266 North Carolina residents and 40% of the 55,749 Iowa residents ever used tobacco. In both men and women, there was a higher prevalence of tobacco use among participants who lived in North Carolina, had less than a high school education, ever drank alcohol, or had a lower intake of fruit and vegetables (Table 1).

The most commonly used tobacco product among men who used any tobacco was cigarettes (84.9%), followed by chewing tobacco (27.3%), cigars (14.2%), cigarillos (11.4%), pipes (9.2%), and snuff (8.1%; Supplementary Table S1). The patterns were slightly different among women who used any tobacco, with nearly all using cigarettes (98.6%), followed by cigarillos (3.1%), chewing tobacco (1.6%), snuff (1.5%), cigars (1.0%), and pipes (0.3%). Fifty-six percent of tobacco users were exclusive users of cigarettes (men, 45.0%; women, 93.4%). Sixty percent of exclusive cigarette smokers were former smokers. A total of 9.5% of tobacco users were exclusive users of smokeless tobacco (men, 12.0%; women, 1.2%), and 2% were exclusive users of other combustible products (2.5%, women: 0.1%). Twenty-five percent of tobacco users were users of cigarettes and at least one other non-cigarette product in their lifetime (men, 30.5%; women, 4.7%). Sixty-six percent of dual users were former cigarette smokers. Use of cigarettes and combustible products (16.3%, men: 20%, women: 3.8%) was higher than use of cigarettes and smokeless tobacco (11.5%; men, 14.6%; women, 1.2%). The highest dually used products were cigarettes and chewing tobacco among men (10.9%) and cigarettes and cigarillos among women (2.9%).

Table 1. Selected characteristics by gender

	Male		Female	
Characteristics	**Never used tobacco *n* (%)**	**Ever used tobacco[a] *n* (%)**	**Never used tobacco *n* (%)**	**Ever used tobacco[a] *n* (%)**
Total ($N = 84,015$)	23,158 (100.0)	29,913 (100.0)	22,047 (100.0)	8,897 (100.0)
Age at enrolment				
<30	2,777 (12.0)	2,642 (8.8)	1,497 (6.8)	475 (5.3)
30–39	6,670 (28.8)	6,373 (21.3)	5,543 (25.1)	2,345 (26.4)
40–49	6,346 (27.4)	8,104 (27.1)	6,190 (28.1)	2,696 (30.3)
50–59	3,969 (17.1)	6,824 (22.8)	5,027 (22.8)	2,208 (24.8)
60–69	2,488 (10.7)	4,612 (15.4)	3,032 (13.8)	960 (10.8)
70+	908 (3.9)	1,358 (4.5)	758 (3.4)	213 (2.4)
State of residence				
Iowa	17,639 (76.2)	17,300 (57.8)	15,573 (70.6)	5,237 (58.9)
North Carolina	5,519 (23.8)	12,613 (42.2)	6,474 (29.4)	3,660 (41.1)
Race				
White	22,636 (97.7)	28,895 (96.6)	21,662 (98.3)	8,656 (97.3)
Black	355 (1.5)	691 (2.3)	242 (1.1)	117 (1.3)
Other	78 (0.3)	211 (0.7)	99 (0.4)	95 (1.1)
Missing	89 (0.4)	116 (0.4)	44 (0.2)	29 (0.3)
Education				
Less than high school	11,954 (51.6)	17,818 (59.6)	8,804 (39.9)	3,805 (42.8)
High school or more	10,744 (46.4)	11,296 (37.8)	11,097 (50.3)	4,084 (45.9)
Other	63 (0.3)	71 (0.2)	1,889 (8.6)	842 (9.5)
Missing	397 (1.7)	728 (2.4)	257 (1.2)	166 (1.9)
BMI kg/m^2				
<18.5	51 (0.2)	83 (0.3)	308 (1.4)	145 (1.6)
18.5–24.9	4,721 (20.4)	5,164 (17.3)	9,198 (41.7)	3,715 (41.8)
25–29.9	8,755 (37.8)	10,826 (36.2)	6,327 (28.7)	2,388 (26.8)
30+	3,804 (16.4)	5,237 (17.5)	3,691 (16.7)	1,417 (15.9)
Missing	5,827 (25.2)	8,603 (28.8)	2,523 (11.4)	1,232 (13.8)
Alcohol drinking year prior enrolment				
Never	7,895 (34.1)	8,384 (28.0)	10,738 (48.7)	3,062 (34.4)
Ever	14,471 (62.5)	20,402 (68.2)	11,110 (50.4)	5,735 (64.5)
Missing	792 (3.4)	1,127 (3.8)	199 (0.9)	100 (1.1)
Usual number of alcohol drinks year prior enrolment				
Never	7,895 (34.1)	8,384 (28.0)	10,738 (48.7)	3,062 (34.4)
≤3 per month	7,737 (33.4)	8,740 (29.2)	9,141 (41.5)	3,927 (44.1)
1–4 per week	5,947 (25.7)	9,064 (30.3)	1,827 (8.3)	1,513 (17.0)
≥5 per week	787 (3.4)	2,598 (8.7)	142 (0.6)	295 (3.3)
Missing	792 (3.4)	1,127 (3.8)	199 (0.9)	100 (1.1)
Fruit intake year prior enrolment (servings per day)				
<1	15,184 (65.6)	21,745 (72.7)	7,106 (32.2)	3,634 (40.8)
1–2	6,438 (27.8)	6,369 (21.3)	8,035 (36.4)	2,617 (29.4)
≥3	519 (2.2)	416 (1.4)	1,435 (6.5)	402 (4.5)
Missing	1,017 (4.4)	1,383 (4.6)	5,471 (24.8)	2,244 (25.2)
Vegetable intake year prior enrolment (servings per day)				
<1	10,973 (47.4)	14,963 (50.0)	4,899 (22.2)	2,249 (25.3)
1–2	9,616 (41.5)	11,198 (37.4)	9,582 (43.5)	3,603 (40.5)
≥3	1,263 (5.5)	1,826 (6.1)	2,047 (9.3)	764 (8.6)
Missing	1,306 (5.6)	1,926 (6.4)	5,519 (25.0)	2,281 (25.6)

Abbreviation: BMI, body mass index.

[a]Ever used one or more of cigarette, pipe, cigar, cigarillo, chewing tobacco, or snuff.

Adjusted mean cigarettes per day, years smoked cigarettes, and cigarette pack-years among exclusive cigarette and dual tobacco users are shown in Supplementary Table S2. Among exclusive cigarette smokers, mean cigarettes per day did not differ considerably between current (14.6 cigarettes per day) and former (14.1 cigarettes per day), but current smokers (21 years) smoked for a longer duration than former smokers (12.5 years). Among the dual tobacco users, current cigarette smokers smoked fewer cigarettes per day but for a longer duration (11.9 cigarettes per day, 19.8 years) than former cigarette smokers (13.3 cigarettes per day, 12.8 years). There was some variation by type of tobacco product. For example, among the dual cigarette–pipe smokers, former cigarette smokers smoked on average 21.7 cigarettes per day for 16 years, whereas current cigarette smokers smoked 5.5 cigarettes per day for 23.7 years. Among the dual cigarette–cigar smokers, former cigarette smokers smoked on average 8.4 cigarettes per day for 9.6 years, whereas current smokers smoked 11.4 cigarettes per day for 24 years. Comparing exclusive cigarette smokers with dual users of any tobacco, there was minimal difference in cigarette frequency and duration.

Exclusive product use and cancer risk

During the follow-up period (median of 16 years), 9,134 incident cancer cases were diagnosed. Of these, 3,401 cases occurred in smoking-related sites: 1,368 gastrointestinal, 789 lung, 645 urinary, and 236 head and neck. Exclusive ever-use of

Table 2. Cancer risk for exclusive use of cigarettes compared with non-tobacco users

	Cigarette smoking status								
	Ever smokers			Former smokers			Current smokers		
Cancer site	Cases	HR[a] (95% CI[a])	P[a]	Cases	HR[a] (95% CI[a])	P[a]	Cases	HR[a] (95% CI[a])	P[a]
Never used tobacco[b]	—	1.00 (—)	—	—	1.00 (—)	—	—	1.00 (—)	—
Total cancers	2,746	1.51 (1.39–1.63)	<0.0001	1,773	1.32 (1.18–1.47)	<0.0001	973	1.71 (1.54–1.89)	<0.0001
Smoking cancers[c]	1,233	2.89 (2.58–3.25)	<0.0001	681	2.28 (1.94–2.70)	<0.0001	542	3.54 (3.08–4.08)	<0.0001
Lung	401	15.48 (11.95–20.06)	<0.0001	139	9.30 (6.56–13.18)	<0.0001	262	23.03 (17.34–30.59)	<0.0001
Gastrointestinal[d]	428	1.64 (1.33–2.03)	<0.0001	296	1.66 (1.26–2.18)	0.0003	132	1.61 (1.21–2.14)	0.001
Urinary[e]	223	2.30 (1.74–3.02)	<0.0001	148	2.28 (1.62–3.22)	<0.0001	75	2.24 (1.55–3.24)	<0.0001
Head neck[f]	88	2.47 (1.55–3.95)	0.0002	43	1.18 (0.50–2.76)	0.71	45	3.63 (2.16–6.12)	<0.0001

	Cigarette smoking duration					
	≤15 years			>15 years		
	Cases	HR[g] (95% CI[g])	P[g]	Cases	HR[g] (95% CI[g])	P[g]
Never used tobacco[b]	—	1.00 (—)	—	—	1.00 (—)	—
Total cancers	1,063	1.33 (0.78–2.28)	0.30	1,584	1.62 (1.48–1.78)	<0.0001
Smoking cancers[c]	355	2.23 (0.89–5.59)	0.09	820	3.44 (3.01–3.93)	<0.0001
Lung	49	21.56 (2.80–66.29)	0.003	338	22.57 (17.16–29.69)	<0.0001
Gastrointestinal[d]	170	1.27 (1.06–1.52)	0.01	242	1.57 (1.21–2.03)	0.001
Urinary[e]	67	3.38 (0.70–16.21)	0.13	147	2.33 (1.67–3.26)	<0.0001
Head neck[f]	27	1.26 (0.77–2.04)	0.36	54	3.38 (2.04–5.62)	<0.0001

	Cigarettes smoked per day					
	≤15 per day			>15 per day		
	Cases	HR[h] (95% CI[h])	P[h]	Cases	HR[h] (95% CI[h])	P[h]
Never used tobacco[b]	—	1.00 (—)	—	—	1.00 (—)	—
Total cancers	1,818	1.58 (1.37–1.82)	<0.0001	841	1.71 (1.52–1.92)	<0.0001
Smoking cancers[c]	744	3.61 (2.99–4.36)	<0.0001	437	3.67 (3.11–4.32)	<0.0001
Lung	208	22.49 (16.10–31.40)	<0.0001	182	29.25 (21.25–40.26)	<0.0001
Gastrointestinal[d]	288	1.49 (1.00–2.22)	0.05	128	1.79 (1.30–2.46)	0.0004
Urinary[e]	129	2.74 (1.74–4.31)	<0.0001	83	2.12 (1.35–3.34)	0.001
Head neck[f]	58	3.66 (1.63–8.18)	0.002	77	3.38 (1.86–6.15)	<0.0001

[a]Adjusted for age, gender, race, state of residence, education, alcohol frequency, cigarettes per day, and years smoked cigarettes.
[b]Reference group: $n = 41{,}026$ controls.
[c]Bladder, colon, cervix, esophagus, kidney, larynx, lip, liver, lung, myeloid leukemia, nasal and sinus, oral cavity, pancreas, pharynx, rectum, stomach, tongue, ureter, and uterine.
[d]Colon, esophagus, liver, pancreas, rectum, and stomach.
[e]Bladder, kidney, and ureter.
[f]Larynx, lip, nasal and sinus, oral cavity, pharynx, and tongue.
[g]Adjusted for age, gender, race, state of residence, education, alcohol frequency, and cigarettes per day.
[h]Adjusted for age, gender, race, state of residence, education, alcohol frequency, and years smoked cigarettes.

cigarettes was associated with increased risks of all cancer sites examined compared with never-use of tobacco (Table 2). For example, ever cigarette smokers compared with never tobacco users had an increased risk of total (HR = 1.51; 95% CI, 1.39–1.63) and smoking-related cancers (HR = 2.89; 95% CI, 2.60–3.25), with the highest relative risk observed for lung cancer (HR = 15.48; 95% CI, 11.95–20.06), followed by head and neck (HR = 2.47; 95% CI, 1.55–3.95), urinary (HR = 2.30; 95% CI, 1.75–3.02), and gastrointestinal cancers (HR = 1.64; 95% CI, 1.33–2.03). About 70% of the head and neck cancers were oral cavity cancers (HR = 1.60; 95% CI, 0.85–2.85). Of the urinary cancers, 63% were bladder (HR = 3.75; 95% CI, 2.64–5.33) and 36% were kidney cancers (HR = 1.09; 95% CI, 0.67–1.79). Of the gastrointestinal cancers, 44% were cancers of the colon (HR = 1.15; 95% CI, 0.82–1.61), 18% rectum (HR = 1.42; 95% CI, 0.89–2.27), 14% pancreas (HR = 2.73; 95% CI, 1.62–4.57), 11% stomach (HR = 2.93; 95% CI, 1.43–5.97), and 9% esophagus (HR = 4.78; 95% CI, 2.36–9.69). For every cancer site or group evaluated, the risks were higher for current than former cigarette smokers. For example, current smokers had a 23-fold risk (95% CI, 17.34–30.59) of lung cancer, whereas former smokers had a 9.3-fold risk (95% CI, 6.56–13.18). This may in part be due to the longer duration of cigarette smoking among current (21.0 years) than former smokers (12.5 years). We also found that that cancer risks were generally higher among those who ever smoked for more than 15 years than those who ever smoked less than 15 years after adjusting for cigarette smoking status. However, the associations were not considerably different when stratified by the mean cigarette smoking frequency (≤15, >15 cigarettes per day).

Exclusive ever-use of other combustible tobacco products (cigars, cigarillos, or pipes) was significantly associated with total (HR = 1.32; 95% CI, 1.10–1.59) and smoking-related cancers (HR = 1.68; 95% CI, 1.21–2.32), including lung cancer (HR = 3.44; 95% CI, 1.53–7.71) compared with never-use of tobacco (Table 3). For the combustible tobacco products, we observed an increased risk for exclusive ever cigar use with total (HR = 1.51; 95% CI, 1.20–1.90) and smoking-related cancers (HR = 1.87; 95% CI, 1.24–2.82), including urinary cancer (HR = 2.50; 95% CI, 1.27–4.93). Of the 9 urinary cancer cases, 5 were bladder (HR = 3.01; 95% CI, 1.20–7.55) and 4 were kidney cancer (HR = 2.12; 95% CI, 0.77–5.83). Exclusive ever-use of pipes was associated with a higher, although not statistically significant, risk of smoking-related cancer (HR = 1.67; 95% CI, 0.92–3.04).

Table 3. Cancer risk for exclusive use of non-cigarette–combustible tobacco products compared with non-tobacco users

	Non-cigarette combustible[a]			Cigar			Cigarillo			Pipe		
Cancer site	Cases	HR[b] (95% CI[b])	P[b]	Cases	HR[b] (95% CI[b])	P[b]	Cases	HR[b] (95% CI[b])	P[b]	Cases	HR[b] (95% CI[b])	P[b]
Never used tobacco[c]	—	1.00	—	—	1.00	—	—	1.00	—	—	1.00	—
Total cancers	121	1.32 (1.10–1.59)	0.003	76	1.51 (1.20–1.90)	0.001	5	1.44 (0.60–3.48	0.41	28	1.13 (0.78–1.64)	0.53
Smoking cancers[d]	40	1.68 (1.21–2.32)	0.002	24	1.87 (1.24–2.82)	0.003	3	—	—	11	1.67 (0.92–3.04)	0.09
Lung	7	3.44 (1.53–7.71)	0.003	3	—	—	0	—	—	3	—	—
Gastrointestinal[e]	18	1.51 (0.94–2.45)	0.09	10	1.58 (0.84–2.98)	0.15	2	—	—	5	1.52 (0.63–3.69)	0.36
Urinary[f]	11	1.66 (0.89–3.08)	0.11	9	2.50 (1.27–4.93)	0.01	0	—	—	2	—	—
Head neck[g]	3	—	—	2	—	—	1	—	—	0	—	—

[a]Ever use of cigars, cigarillos, and/or pipes.
[b]Adjusted for age, gender, race, state of residence, education, and alcohol frequency.
[c]Reference group: $n = 41{,}026$ controls.
[d]Bladder, colon, cervix, esophagus, kidney, larynx, lip, liver, lung, myeloid leukemia, nasal and sinus, oral cavity, pancreas, pharynx, rectum, stomach, tongue, ureter, and uterine.
[e]Colon, esophagus, liver, pancreas, rectum, and stomach.
[f]Bladder, kidney, and ureter.
[g]Larynx, lip, nasal and sinus, oral cavity, pharynx, and tongue.

Exclusive ever-use of smokeless tobacco (chewing tobacco or snuff) was significantly associated with smoking-related cancers (HR = 1.27; 95% CI, 1.00–1.62), including lung (HR = 2.21; 95% CI, 1.11–4.42) and gastrointestinal (HR = 1.38; 95% CI, 1.00–1.92) compared with never-use of tobacco (Table 4). Of the 41 smokeless tobacco users with gastrointestinal cancers, 19 were cancers of the colon (HR = 1.33; 95% CI, 0.82–2.16), 10 rectum (HR = 1.37; 95% CI, 0.70–2.71), 4 pancreas (HR = 1.18; 95% CI, 0.41–3.36), 4 liver, 3 stomach, and 1 esophagus. Of the 9 head and neck cancers, 8 were oral cavity (HR = 1.54; 95% CI, 0.68–3.46). By smokeless tobacco product, exclusive ever-use of chewing tobacco was associated with smoking-related cancer, including lung (HR = 2.20; 95% CI, 0.98–4.98) and head and neck cancers (HR = 2.08; 95% CI, 0.97–4.47). Exclusive ever-use of snuff was associated with gastrointestinal cancer (HR = 2.09; 95% CI, 1.20–3.64). Exclusive smokeless tobacco use was not associated with urinary cancers.

Dual-product use and cancer risk

Compared with exclusive cigarette smokers, ever cigarette smokers who additionally used another combustible tobacco in their lifetime had higher risks of smoking-related cancers (HR = 1.16; 95% CI, 1.04–1.30), including lung cancer (HR = 1.32; 95% CI, 1.09–1.60; Table 5). Risks did not appear to differ for former or current cigarette smokers. Stratified by cigarette smoking duration, there were significant increases in risk among those who ever smoked cigarettes for more than 15 years: total cancers (HR = 1.11; 95% CI, 1.00–1.22), smoking-related cancers (HR = 1.19; 95% CI, 1.04–1.36), lung cancer (HR = 1.29; 95% CI, 1.05–1.58), and gastrointestinal cancers (HR = 1.27; 95% CI, 1.01–1.61; Table 6). Of the gastrointestinal cancers, 42% were colon cancers (HR = 1.39; 95% CI, 1.00–2.01) and 16% were pancreatic cancer (HR = 1.80; 95% CI, 0.97–3.32). Among the combustible products, dual cigarette–cigarillo users had the highest and most consistent risks, which were stronger risks among those that smoked cigarettes for more than 15 years. In contrast, dual cigarette–pipe users had a higher risk of cancer among former cigarette smokers and participants that smoked cigarettes for less than 15 years. There were no discernable patterns for dual cigarette-combustible tobacco use when stratified by cigarettes per day. Dual cigarette-smokeless tobacco users generally had cancer risks similar to exclusive cigarette smokers regardless of cigarette smoking status, cigarette smoking duration, or frequency.

Discussion

In this large U.S.-based agricultural cohort, exclusive users of cigarettes, other combustible tobacco, and smokeless tobacco had higher risks of lung and other cancer compared with non-tobacco users. Participants who ever smoked cigarettes and at least one

Table 4. Cancer risk for exclusive use of smokeless tobacco compared with non-tobacco users

	Smokeless tobacco[a]			Chewing tobacco			Snuff		
Cancer site	Cases	HR[b] (95% CI[b])	P[b]	Cases	HR[b] (95% CI[b])	P[b]	Cases	HR[b] (95% CI[b])	P[b]
Never used tobacco[c]	—	1.00	—	—	1.00	—	—	1.00	—
Total cancers	228	0.97 (0.85–1.12)	0.71	175	1.02 (0.87–1.20)	0.78	44	0.92 (0.68–1.25)	0.58
Smoking cancers[d]	79	1.27 (1.00–1.62)	0.05	58	1.29 (0.98–1.71)	0.07	18	1.34 (0.83–2.17)	0.24
Lung	10	2.21 (1.11–4.42)	0.02	7	2.20 (0.98–4.97)	0.06	3	—	—
Gastrointestinal[e]	41	1.38 (1.00–1.92)	0.05	27	1.25 (0.83–1.86)	0.28	13	2.09 (1.20–3.64)	0.01
Urinary[f]	15	0.87 (0.49–1.54)	0.63	12	0.97 (0.52–1.81)	0.93	1	—	—
Head neck[g]	9	1.54 (0.72–3.3)	0.26	9	2.08 (0.97–4.47)	0.06	0	—	—

[a]Ever use of chewing tobacco and/or snuff.
[b]Adjusted for age, gender, race, state of residence, education, and alcohol frequency.
[c]Reference group: $n = 41{,}026$ controls.
[d]Bladder, colon, cervix, esophagus, kidney, larynx, lip, liver, lung, myeloid leukemia, nasal and sinus, oral cavity, pancreas, pharynx, rectum, stomach, tongue, ureter, and uterine.
[e]Colon, esophagus, liver, pancreas, rectum, and stomach.
[f]Bladder, kidney, and ureter.
[g]Larynx, lip, nasal and sinus, oral cavity, pharynx, and tongue.

Table 5. Cancer risk for dual tobacco use[a] compared with exclusive cigarette use

	Cigarette smoking status								
	Ever			Former			Current		
Cancer site	Cases	HR[b] (95% CI[b])	P[b]	Cases	HR[b] (95% CI[b])	P[b]	Cases	HR[b] (95% CI[b])	P[b]
Exclusive cigarette smokers[c]	—	1.00	—	—	1.00	—	—	1.00	—
Cigarette-other combustible tobacco[d]									
Total cancers	1,090	1.08 (1.00–1.17)	0.06	758	1.08 (0.98–1.19)	0.11	332	1.09 (0.95–1.24)	0.26
Smoking cancers[e]	533	1.16 (1.04–1.30)	0.01	325	1.15 (0.99–1.33)	0.07	208	1.18 (1.00–1.42)	0.06
Lung	195	1.32 (1.09–1.60)	0.01	104	1.68 (1.25–2.25)	0.001	91	1.09 (0.84–1.42)	0.51
Gastrointestinal[f]	185	1.12 (0.92–1.36)	0.25	121	0.98 (0.77–1.24)	0.86	64	1.53 (1.10–2.14)	0.01
Urinary[g]	98	1.07 (0.82–1.39)	0.63	69	1.03 (0.75–1.40)	0.92	29	1.09 (0.69–1.74)	0.71
Head neck[h]	39	1.27 (0.84–1.92)	0.26	20	1.39 (0.75–2.57)	0.29	19	1.20 (0.68–2.10)	0.54
Cigarette-cigar									
Total cancers	293	1.03 (0.90–1.17)	0.71	204	0.98 (0.83–1.16)	0.85	89	1.14 (0.90–1.43)	0.29
Smoking cancers[e]	143	1.11 (0.92–1.34)	0.29	85	0.99 (0.77–1.28)	0.96	58	1.30 (0.98–1.74)	0.08
Lung	49	1.26 (0.91–1.74)	0.17	26	1.44 (0.89–2.33)	0.14	23	1.13 (0.73–1.77)	0.59
Gastrointestinal[f]	62	1.27 (0.95–1.70)	0.11	42	1.06 (0.74–1.52)	0.74	20	2.03 (1.23–3.38)	0.01
Urinary[g]	23	0.85 (0.53–1.38)	0.51	11	0.55 (0.28–1.09)	0.09	12	1.48 (0.73–2.96)	0.26
Head neck[h]	7	0.70 (0.30–1.64)	0.41	4	0.74 (0.22–2.47)	0.62	3	—	—
Cigarette-cigarillo									
Total cancers	422	1.15 (1.03–1.28)	0.01	230	1.20 (1.03–1.39)	0.02	192	1.09 (0.93–1.29)	0.29
Smoking cancers[e]	226	1.28 (1.09–1.49)	0.002	110	1.41 (1.13–1.76)	0.002	116	1.17 (0.94–1.45)	0.16
Lung	86	1.29 (1.00–1.66)	0.05	35	1.84 (1.21–2.79)	0.004	51	1.08 (0.78–1.50)	0.63
Gastrointestinal[f]	80	1.39 (1.07–1.80)	0.01	44	1.36 (0.97–1.91)	0.07	36	1.47 (0.98–2.23)	0.06
Urinary[g]	31	1.02 (0.68–1.52)	0.93	18	1.06 (0.63–1.80)	0.82	13	0.94 (0.51–1.72)	0.84
Head neck[h]	18	1.48 (0.87–2.51)	0.15	5	1.53 (0.58–4.00)	0.40	13	1.50 (0.78–2.81)	0.22
Cigarette-pipe									
Total cancers	196	1.11 (0.95–1.30)	0.19	170	1.15 (0.97–1.36)	0.11	26	0.94 (0.62–1.41)	0.75
Smoking cancers[e]	88	1.14 (0.90–1.44)	0.29	75	1.23 (0.95–1.60)	0.12	13	0.75 (0.41–1.37)	0.34
Lung	33	1.56 (1.05–2.33)	0.03	26	2.21 (1.38–3.53)	0.001	7	0.70 (0.29–1.72)	0.44
Gastrointestinal[f]	18	0.59 (0.35–0.97)	0.04	16	0.59 (0.34–1.01)	0.05	2	—	—
Urinary[g]	27	1.52 (0.98–2.34)	0.06	26	1.61 (1.02–2.53)	0.04	1	—	—
Head Neck[h]	8	1.75 (0.82–3.73)	0.15	6	1.81 (0.73–4.49)	0.20	2	—	—
Cigarette-smokeless tobacco[i]									
Total cancers	493	0.97 (0.87–1.08)	0.59	417	1.01 (0.89–1.13)	0.92	76	0.82 (0.64–1.05)	0.11
Smoking cancers[e]	209	0.94 (0.80–1.11)	0.48	166	0.99 (0.82–1.20)	0.92	43	0.82 (0.59–1.14)	0.23
Lung	54	0.80 (0.57–1.11)	0.17	40	1.00 (0.66–1.50)	0.88	14	0.50 (0.27–0.92)	0.03
Gastrointestinal[f]	90	1.04 (0.80–1.34)	0.79	75	0.99 (0.75–1.32)	0.90	15	1.19 (0.70–2.09)	0.54
Urinary[g]	46	1.09 (0.78–1.55)	0.63	38	1.17 (0.79–1.75)	0.67	8	0.96 (0.45–2.05)	0.92
Head neck[h]	15	0.88 (0.47–1.62)	0.67	9	0.73 (0.31–1.73)	0.48	6	1.08 (0.44–2.61)	0.87
Cigarette-chewing tobacco									
Total cancers	381	0.98 (0.87–1.11)	0.77	323	1.03 (0.90–1.18)	0.68	58	0.79 (0.59–1.04)	0.10
Smoking cancers[e]	169	0.96 (0.80–1.15)	0.65	136	1.04 (0.84–1.29)	0.73	33	0.76 (0.52–1.12)	0.19
Lung	45	0.81 (0.56–1.16)	0.24	35	1.11 (0.71–1.72)	0.65	10	0.41 (0.19–0.87)	0.02
Gastrointestinal[f]	73	1.08 (0.82–1.44)	0.58	61	1.05 (0.76–1.45)	0.76	12	1.18 (0.63–2.19)	0.60
Urinary[g]	36	1.08 (0.72–1.60)	0.72	30	1.20 (0.77–1.89)	0.43	6	0.89 (0.38–2.11)	0.79
Head neck[h]	13	0.98 (0.50–1.90)	0.94	8	0.85 (0.34–2.13)	0.72	5	1.17 (0.45–3.04)	0.75
Cigarette-snuff									
Total cancers	95	0.98 (0.79–1.22)	0.88	79	0.97 (0.76–1.23)	0.78	16	1.05 (0.63–1.76)	0.85
Smoking cancers[e]	35	0.96 (0.68–1.36)	0.83	26	0.90 (0.60–1.35)	0.60	9	1.21 (0.62–2.35)	0.57
Lung	8	0.86 (0.41–1.84)	0.70	5	0.86 (0.31–2.36)	0.77	3	—	—
Gastrointestinal[f]	14	0.91 (0.53–1.56)	0.73	11	0.82 (0.44–1.50)	0.51	3	—	—
Urinary[g]	10	1.32 (0.69–2.53)	0.40	8	1.23 (0.59–2.55)	0.58	2	—	—
Head neck[h]	1	—	—	0	—	—	1	—	—

[a]Cigarette smokers who ever used another tobacco product.
[b]Adjusted for age, gender, race, state of residence, education, alcohol frequency, cigarettes per day, and years smoked cigarettes.
[c]Reference for ever smokers = 19,009; former smokers = 11,379; current smokers = 7,603.
[d]Cigarette smokers who ever used cigars, cigarillos, and/or pipes.
[e]Bladder, colon, cervix, esophagus, kidney, larynx, lip, liver, lung, myeloid leukemia, nasal and sinus, oral cavity, pancreas, pharynx, rectum, stomach, tongue, ureter, and uterine.
[f]Colon, esophagus, liver, pancreas, rectum, and stomach.
[g]Bladder, kidney, and ureter.
[h]Larynx, lip, nasal and sinus, oral cavity, pharynx, and tongue.
[i]Cigarette smokers who ever used chewing tobacco and/or snuff.

other combustible tobacco product in their lifetime had higher total and smoking-related cancer risks than exclusive cigarette smokers, with the strongest additional risk among those who smoked cigarettes for more than 15 years.

Our findings for exclusive cigarette smoking are consistent with the extensive published literature identifying cigarette smoking as one of the primary causes of cancer (8, 12). The higher risks among current exclusive cigarette smokers seem to be linked to the

Table 6. Cancer risk for dual tobacco use[a] compared with exclusive cigarette use

	Cigarette smoking duration						Cigarette smoking frequency					
	≤15 years			>15 years			≤15 cigarettes per day			>15 cigarettes per day		
	Cases	HR[b] (95% CI[b])	P[b]	Cases	HR[b] (95% CI[b])	P[b]	Cases	HR[c] (95% CI[c])	P[c]	Cases	HR[c] (95% CI[c])	P[c]
Exclusive cigarette smokers[d]	—	1.00	—	—	1.00	—	—	1.00	—	—	1.00	—
Cigarette-other combustible tobacco[e]												
Total cancers	389	1.04 (0.91–1.18)	0.57	678	1.11 (1.00–1.22)	0.04	683	1.08 (0.98–1.19)	0.12	368	1.08 (0.95–1.23)	0.26
Smoking cancers[f]	139	1.10 (0.88–1.37)	0.39	380	1.19 (1.04–1.36)	0.01	307	1.14 (0.99–1.33)	0.08	208	1.20 (1.01–1.43)	0.04
Lung	26	1.57 (0.92–2.70)	0.10	163	1.29 (1.05–1.58)	0.02	102	1.43 (1.10–1.87)	0.01	84	1.21 (0.92–1.60)	0.17
Gastrointestinal[g]	57	0.88 (0.63–1.23)	0.44	122	1.27 (1.01–1.61)	0.05	113	1.01 (0.79–1.29)	0.91	68	1.31 (0.96–1.80)	0.09
Urinary[h]	37	1.27 (0.82–1.98)	0.28	59	0.97 (0.70–1.35)	0.85	62	1.14 (0.82–1.59)	0.44	32	0.95 (0.62–1.48)	0.83
Head neck[i]	12	1.05 (0.48–2.27)	0.90	27	1.37 (0.84–2.24)	0.21	21	1.15 (0.67–1.97)	0.62	17	1.44 (0.76–2.75)	0.26
Cigarette-cigar												
Total cancers	127	1.03 (0.84–1.26)	0.78	156	1.03 (0.86–1.22)	0.76	193	1.04 (0.89–1.23)	0.61	86	0.99 (0.79–1.26)	0.95
Smoking cancers[f]	48	1.12 (0.80–1.57)	0.51	90	1.11 (0.88–1.4)	0.37	89	1.13 (0.89–1.43)	0.33	48	1.10 (0.80–1.50)	0.56
Lung	9	1.91 (0.86–4.22)	0.11	38	1.18 (0.83–1.68)	0.37	27	1.42 (0.92–2.20)	0.12	20	1.07 (0.65–1.74)	0.80
Gastrointestinal[g]	26	1.10 (0.70–1.73)	0.69	34	1.39 (0.95–2.04)	0.09	42	1.21 (0.85–1.73)	0.30	19	1.43 (0.86–2.37)	0.17
Urinary[h]	8	0.82 (0.37–1.84)	0.64	14	0.87 (0.48–1.58)	0.65	15	0.87 (0.48–1.57)	0.64	6	0.83 (0.36–1.94)	0.67
Head neck[i]	4	1.02 (0.30–3.50)	0.98	3	—	—	3	—	—	3	—	—
Cigarette-cigarillo												
Total cancers	106	1.03 (0.84–1.28)	0.76	309	1.20 (1.05–1.36)	0.01	250	1.14 (0.99–1.31)	0.08	163	1.17 (0.98–1.40)	0.08
Smoking cancers[f]	44	1.22 (0.87–1.72)	0.25	177	1.29 (1.09–1.53)	0.004	122	1.23 (1.00–1.52)	0.05	99	1.33 (1.05–1.67)	0.02
Lung	7	1.19 (0.49–2.87)	0.70	76	1.30 (0.99–1.60)	0.06	44	1.37 (0.96–1.96)	0.08	39	1.22 (0.85–1.76)	0.28
Gastrointestinal[g]	20	1.08 (0.64–1.80)	0.78	58	1.52 (1.24–2.06)	0.01	45	1.25 (0.89–1.75)	0.21	33	1.59 (1.06–2.37)	0.02
Urinary[h]	9	1.30 (0.63–2.67)	0.48	22	0.94 (0.58–1.51)	0.79	19	1.10 (0.66–1.82)	0.73	12	0.91 (0.48–1.75)	0.78
Head neck[i]	3	—	—	15	1.64 (0.91–2.96)	0.10	8	1.17 (0.54–2.52)	0.69	10	1.77 (0.84–3.73)	0.14
Cigarette-pipe												
Total cancers	86	1.24 (0.98–1.57)	0.08	104	1.03 (0.84–1.27)	0.78	129	1.14 (0.94–1.38)	0.17	58	1.05 (0.80–1.39)	0.71
Smoking cancers[f]	26	1.18 (0.78–1.78)	0.44	58	1.10 (0.83–1.47)	0.52	54	1.17 (0.87–1.57)	0.29	29	1.07 (0.72–1.59)	0.72
Lung	6	2.30 (0.93–5.75)	0.07	26	1.43 (0.91–2.24)	0.12	15	1.44 (0.82–2.54)	0.21	15	1.74 (0.99–3.06)	0.06
Gastrointestinal[g]	6	0.55 (0.25–1.28)	0.17	10	0.60 (0.31–1.14)	0.12	12	0.58 (0.31–1.07)	0.08	5	0.60 (0.24–1.48)	0.27
Urinary[h]	11	1.95 (0.99–3.82)	0.05	15	1.29 (0.73–2.28)	0.39	18	1.71 (1.01–2.91)	0.05	8	1.16 (0.54–2.48)	0.70
Head neck[i]	2	—	—	6	1.86 (0.77–4.52)	0.17	8	2.62 (1.19–5.78)	0.02	0	—	—
Cigarette-smokeless tobacco[j]												
Total cancers	233	1.00 (0.86–1.17)	0.92	244	0.95 (0.82–1.10)	0.47	326	0.94 (0.82–1.07)	0.36	152	1.05 (0.87–1.27)	0.58
Smoking cancers[f]	89	1.13 (0.85–1.47)	0.37	113	0.85 (0.69–1.06)	0.13	125	0.87 (0.70,1.08)	0.21	77	1.08 (0.83–1.41)	0.56
Lung	8	0.64 (0.24–1.67)	0.36	44	0.82 (0.58–1.16)	0.29	26	0.68 (0.42–1.09)	0.11	26	0.97 (0.61–1.53)	0.88
Gastrointestinal[g]	52	1.36 (0.95–1.30)	0.09	35	0.80 (0.55–1.17)	0.21	60	1.00 (0.73–1.36)	0.99	26	1.14 (0.72–1.78)	0.58
Urinary[h]	17	1.03 (0.57–1.87)	0.91	28	1.10 (0.71–1.70)	0.65	27	0.93 (0.59–1.47)	0.76	18	1.33 (0.76–2.31)	0.32
Head neck[i]	9	1.18 (0.50–2.79)	0.71	5	0.66 (0.25–1.65)	0.35	10	0.81 (0.37–1.78)	0.60	5	1.00 (0.37–2.71)	1.00
Cigarette-chewing tobacco												
Total cancers	176	1.05 (0.87–1.25)	0.63	193	0.94 (0.79–1.10)	0.42	251	0.95 (0.82–1.10)	0.49	118	1.08 (0.87–1.32)	0.49
Smoking cancers[f]	68	1.16 (0.86–1.57)	0.33	94	0.86 (0.68–1.09)	0.22	102	0.90 (0.71–1.14)	0.40	61	1.08 (0.80–1.45)	0.63
Lung	7	0.73 (0.25–2.12)	0.56	36	0.81 (0.55–1.20)	0.30	22	0.68 (0.41–1.15)	0.15	22	0.99 (0.60–1.64)	0.96
Gastrointestinal[g]	39	1.38 (0.92–2.06)	0.12	31	0.87 (0.58–1.31)	0.50	48	1.04 (0.74–1.47)	0.82	21	1.20 (0.73–1.97)	0.48
Urinary[h]	12	0.96 (0.47–1.93)	0.90	23	1.12 (0.70–1.81)	0.64	23	1.03 (0.63–1.69)	0.91	12	1.09 (0.56–2.11)	0.81
Head neck[i]	8	1.43 (0.57–3.57)	0.44	4	0.66 (0.23–1.88)	0.43	8	0.79 (0.33–1.94)	0.61	5	1.31 (0.48–3.58)	0.59
Cigarette-snuff												
Total cancers	48	0.97 (0.72–1.30)	0.81	43	0.92 (0.57–1.50)	0.75	65	0.96 (0.74–1.25)	0.77	27	1.04 (0.70–1.54)	0.85
Smoking cancers[f]	17	1.01 (0.62–1.67)	0.96	18	1.03 (0.45–2.32)	0.95	19	0.80 (0.50–1.27)	0.34	15	1.31 (0.77–2.21)	0.32
Lung	1	—	—	7	0.57 (0.21–1.54)	0.26	4	0.89 (0.32–2.43)	0.82	3	—	—
Gastrointestinal[g]	10	1.20 (0.63–2.30)	0.58	4	1.21 (0.49–2.99)	0.69	9	0.78 (0.40–1.53)	0.46	5	1.28 (0.51–3.17)	0.60
Urinary[h]	5	1.39 (0.54–3.56)	0.49	5	0.75 (0.10–5.53)	0.77	4	0.76 (0.28–2.08)	0.59	6	2.51 (1.06–5.94)	0.04
Head neck[i]	0	—	—	1	—	—	1	—	—	0	—	—

[a]Cigarette smokers who ever used another tobacco product.
[b]Adjusted for age, gender, race, state of residence, education, alcohol frequency, and cigarettes per day.
[c]Adjusted for age, gender, race, state of residence, education, alcohol frequency, and years smoked cigarettes.
[d]Reference for ≤15 years = 10,545; >15 years = 7,970; ≤15 cigarettes per day = 13,748; >15 cigarettes per day = 4,823.
[e]Cigarette smokers who ever used cigars, cigarillos, and/or pipes.
[f]Bladder, colon, cervix, esophagus, kidney, larynx, lip, liver, lung, myeloid leukemia, nasal and sinus, oral cavity, pancreas, pharynx, rectum, stomach, tongue, ureter, and uterine.
[g]Colon, esophagus, liver, pancreas, rectum, and stomach.
[h]Bladder, kidney, and ureter.
[i]Larynx, lip, nasal and sinus, oral cavity, pharynx, and tongue.
[j]Cigarette smokers who ever used chewing tobacco and/or snuff.

longer average smoking duration among current (21 years) versus former (12.5 years) smokers, rather than to differences in the number of cigarettes smoked per day. This is consistent with previous epidemiologic and laboratory studies reporting cigarette smoking duration to be a stronger predictor of cancer risk than smoking frequency (13–16).

Exclusive use of other combustible tobacco products was most strongly associated with lung cancer. This is in line with results from a multicenter case–control study in Europe that reported 8- to 9-fold risks of lung cancer for exclusive use of pipes and cigars/cigarillos, respectively (17). It was also reported that lung cancer risk is higher among cigar smokers who report inhaling the smoke than not inhaling, and higher among cigar smokers who previously smoked cigarettes than among those who only smoked cigars (18). Our finding for an association between exclusive cigar use and urinary cancers (bladder, kidney) is consistent with a pooled study among European men that found a significant 2-fold risk in bladder cancer among exclusive cigar smokers (19), and the European Prospective Investigation into Cancer and Nutrition (EPIC) that found a nonsignificant 1.5-fold bladder risk (20). The EPIC study also reported a nonsignificant 1.2-fold risk for cigar smoking and kidney cancer (20). Studies specifically examining exclusive use of non-cigarette–combustible products are limited.

The strongest association for exclusive use of smokeless tobacco was also for lung cancer. This finding is biologically plausible given that tobacco-specific nitrosamines (TSNA) are found in smokeless tobacco at high concentrations (21–23). In a study of 182 U.S. male smokeless tobacco users, Hecht and colleagues showed that urinary levels of the nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-(butanol) (NNAL) were higher in smokeless tobacco users than in cigarette smokers (23). Laboratory studies have shown that treatment of rats with TSNA by injection or administration in the drinking water can cause lung cancer. Particularly, (methylnitrosamino)-1-(3-pyridyl)-1-(butanone), which is found in smokeless tobacco, and its major metabolite, NNAL, are lung carcinogens in rats (24–26). Epidemiologic data on smokeless tobacco and lung cancer are somewhat inconsistent. For example, a previous study conducted using The National Health and Nutrition Examination Survey found a significant association between exclusive smokeless tobacco use and lung cancer among women, but not men (27). In the American Cancer Society cohorts, smokeless tobacco was linked to lung cancer mortality in the Cancer Prevention Study (CPS)-II, but not CPS-I (28). Two studies of snus (moist form of snuff) use in Europe reported null associations between smokeless tobacco and lung cancer after accounting for cigarette smoking (29, 30), as did a case–control study of moderate or heavy chewing tobacco or snuff (31). Reasons for the inconsistent findings for smokeless tobacco are unclear, but may be linked to variations in the prevalence of smokeless tobacco use in the population, frequency, and duration of use, as well as use of other tobacco products and unmeasured confounding. In their last review, IARC reported insufficient evidence for an association between smokeless tobacco and lung cancer, but did report sufficient evidence linking smokeless tobacco with cancers of the pancreas, oral cavity, and esophagus (8, 32).

In this study, we also found increased risks of gastrointestinal (colon, rectum, pancreas) and head and neck (oral cavity) cancers with exclusive smokeless tobacco use. Several studies have reported associations between smokeless tobacco and pancreatic cancer (33–37), and laboratory studies that have shown associations TSNA and pancreatic tumors in rats (24–26). To our knowledge, only one previous study has reported a link between high snus use and left-sided colon cancer in a Swedish male population (38). Some of the strongest reported associations for smokeless tobacco have been with oral and pharyngeal cancers. For example, Boffetta and colleagues reported a significant relative risk of 1.8 pooled from 11 studies (36), and Lee and colleagues reported a significant 1.4 relative risk pooled from 40 studies (37). Consistent with these epidemiologic findings, laboratory studies have suggested that TSNAs, in particular *N*-nitrosonornicotine, are responsible for cytogenic damage in oral epithelial cells (22, 39, 40).

For dual tobacco product use, our results indicate that ever users of cigarettes and other combustible tobacco products had higher risks of total and certain smoking-related cancers compared with exclusive cigarette smokers. In contrast, ever users of cigarettes and smokeless tobacco had risks similar to exclusive cigarette use. This is consistent with a previous review article that concluded there was no additional cancer risk for dual cigarette-smokeless tobacco use compared with exclusive cigarette use, although the epidemiologic data to evaluate this were limited (41). Reasons for the different cancer risks between the dual cigarette-combustible and cigarette-smokeless tobacco are unknown, but may be related to observed differences in cigarette smoking patterns. Also, current/former status, duration, and frequency of use of the non-cigarette products may also play a role, but as we did not have these data for non-cigarette products, we could not determine whether dual use was concurrent or sequential. Also, factors related to nicotine addiction (e.g. time-to-first cigarette), tobacco cessation (e.g. duration since cessation, number of times tried to quit), or changing the type of tobacco product could also be linked to differences in cancer risks.

In this U.S. agricultural population, the prevalence of cigarette smoking at enrolment (1993–1997) was somewhat lower (40.7% ever, 14.6% current) than the general U.S. population (47% ever, 25% current; ref. 42). AHS smokers also smoked somewhat less (∼14 cigarettes per day) than the average U.S. smoker in mid-1990s (∼18 cigarettes per day; ref. 43). Use of non-cigarette–combustible products in the AHS was about the same as the U.S. population in the mid-1990s (∼8% of males; ref. 18). In contrast, the use of smokeless tobacco was higher in the AHS (11.8% ever use of chewing tobacco/ snuff) than the general U.S. population (3%–6% ever use of chewing tobacco/snuff/dip; ref. 44). Higher use of smokeless tobacco in rural/agricultural populations has been noted, particularly among men (3). As the participants in this occupational cohort are predominantly male and white, and tobacco use is almost 50% higher among men than women, we could not examine associations among women or non-whites with adequate statistical power.

This is one of the first studies to evaluate cancer incidence in relation to exclusive and dual use of multiple types of tobacco products. Smokeless tobacco use is often understudied compared with other tobacco products due to its lower prevalence of use; however, in this U.S. agricultural study population, the prevalence of smokeless tobacco use was higher than the general U.S. population; thus, we had a sufficient number of exposed cases to evaluate its exclusive use and dual use with cigarettes. However, our analysis of non-cigarette tobacco products was limited to ever versus never for both exclusive and dual use. Therefore, we could neither analyze their duration or frequency of use nor could we determine whether they were used concurrently with cigarettes.

We found that exclusive use of smokeless tobacco as well as cigarettes and other combustible tobacco was most strongly associated with lung cancer. In addition, we found that dual users of cigarettes and other combustible products had higher cancer risks than exclusive cigarette users, whereas dual users of cigarettes and smokeless tobacco generally had similar risks to exclusive

cigarette users. Future studies designed to evaluate the frequency, duration, and other characteristics of smokeless tobacco and non-cigarette–combustible tobacco use are needed to better evaluate their associations with cancer risk.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): G. Andreotti, M.C. Alavanja, D.P. Sandler, L.B. Freeman
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Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): G. Andreotti
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