Research Article

Cancer Epidemiology, Biomarkers & Prevention

Associations of Tobacco and Alcohol Use with Risk of Neuroendocrine Tumors of the Small Intestine in Utah

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Abstract

Background: Incidence of small-intestine neuroendocrine tumors (SINT) has been increasing in the United States over the past 40 years, with higher incidence in Utah than elsewhere. As information about how these tumors arise is limited, elucidating lifestyle factors associated with SINT in a statewide cohort could potentially identify those at risk to help mitigate their effects.

Methods: Cases of SINT with a carcinoid histology (8240 or 8241) diagnosed in Utah from 1996 to 2014 with no prior history of cancer within 5 years ($n = 433$) were matched to population controls (1:10 ratio). Tobacco and alcohol exposures before case diagnosis were identified from International Classification of Diseases codes in statewide medical records and from self-reported data captured at patient encounters beginning in 1996. Multivariate logistic regression was used to estimate risk of SINT associated with tobacco and alcohol in cases compared with controls.

Results: An increased risk of SINT was observed in tobacco-exposed individuals compared with unexposed [OR, 1.44; 95% confidence interval (CI), 1.11–1.86; $P = 0.006$]. Those who were exposed to alcohol exhibited an increased risk of SINT (OR, 1.62; 95% CI, 1.05–2.49; $P = 0.03$).

Conclusions: This study supports tobacco and alcohol use as risk factors for SINT, independent of family history. However, low rates of smoking and alcohol use in Utah coupled with higher rates of SINT suggest other factors may contribute to development of these tumors.

Impact: Although tobacco and alcohol modestly contribute to risk, our study suggests in addition to greater detection of tumors, other as-of-yet undefined exposures may drive rising SINT incidence.

Introduction

Neuroendocrine tumors of the small intestine are tumors that derive from enterochromaffin cells of the neuroendocrine system in the gut. These cells contain a large amount of the body's store of serotonin and, in response to stimuli in the lumen (chemical, mechanical, and pathological), the release of serotonin regulates gut motility and secretion as well as triggering nausea signals to the brain (1). Approximately 40% of all tumors of the small intestine are carcinoids (2–4). Although relatively rare (0.9–1.1 per 100,000 U.S. population per year based on current estimates), incidence of these small-intestine neuroendocrine tumors (SINT) has been increasing in the United States over the past 40 years (5–8). According to data from the National Cancer Institute's Surveillance Epidemiology and End Results Program (SEER; www.seer.cancer.gov/seerstat), incidence of SINT in Utah has been increasing at a faster rate than elsewhere in the nation (Fig. 1). The reasons for this trend are not yet fully understood; however, the steady rise in SINT incidence has been attributed to increased detection of early-stage disease from greater use of clinical imaging procedures (8).

Information about how these tumors arise is limited. We demonstrated a significant familial risk of SINT in close (first-degree) as well as more distant relatives of patients with SINT, supporting both a genetic and environmental component to these tumors (9). Lifestyle factors, such as tobacco exposure from cigarette smoking and alcohol consumption, have also been implicated as promoters of risk of neuroendocrine tumors. In a systematic review of risk factors for neuroendocrine neoplasms, Leoncini and colleagues (10) reported a summary estimate of a significant 1.6-fold increased risk of SINT in ever versus never smokers based on two case–control studies in the United States and one in Europe, whereas Haugvik and colleagues (11) reported a similar 1.4-fold risk of SINT in ever-smokers based on three U.S. and two European populations. With regard to alcohol consumption, a meta-association of ever versus never alcohol consumption was not significant in either systematic review (10, 11). In a recent prospective case–control investigation of risk factors for SINT in Europe (215 patients and 860 controls), Rinzivillo and colleagues (12) reported that smoking conferred a significant 1.5-fold risk for small-intestine carcinoid cancer which in heavy smokers

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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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Cancer Epidemiol Biomarkers Prev 2019;28:1998–2004

doi: 10.1158/1055-9965.EPI-19-0465

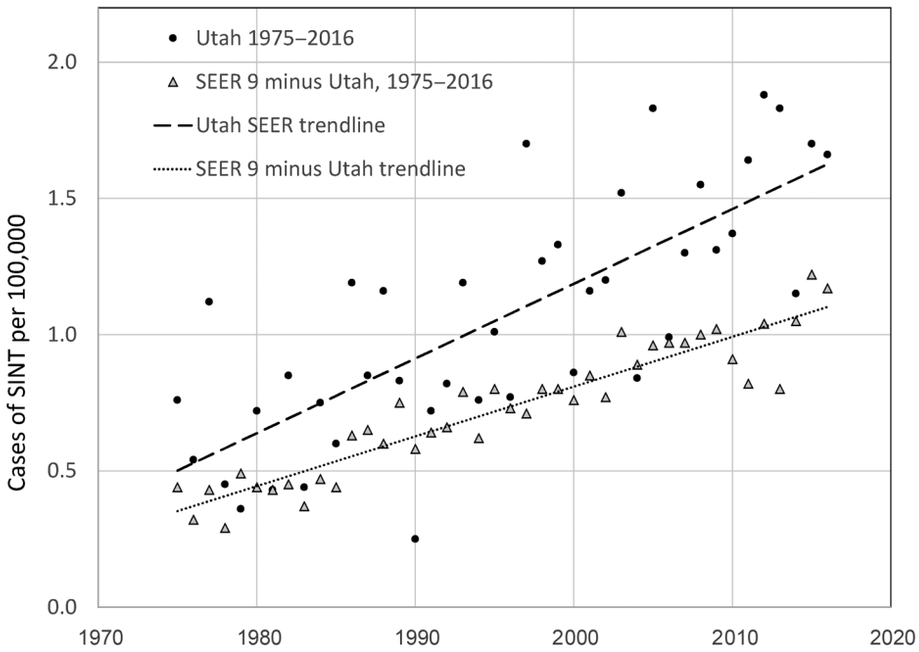

Figure 1.
Cases of SINT per 100,000 population from 1975 to 2016 in Utah compared with other SEER registries. Rates are age-adjusted to the 2000 U.S. Standard Population standard using the Surveillance Research Program, National Cancer Institute SEER*Stat software version 8.3.5 (www.seer.cancer.gov/seerstat). SEER 9 data are limited to all registries with data going back to 1975, which includes Connecticut, Iowa, New Mexico, Hawaii, and the metropolitan areas of Detroit, Atlanta, San Francisco-Oakland, and the 13-county Seattle-Puget Sound area.

was higher, 1.9-fold. They also reported that although the proportion of ever alcohol drinkers did not differ between patients and controls, patients were twice as likely to have an intake of >21 drinks per week. Though significant in a univariate analysis, high alcohol consumption was not associated in a multivariate model (12).

Only a limited number of studies have assessed lifestyle factors of smoking and alcohol in association with SINT and it has been suggested that further studies are needed for confirmation and clarification of these risk factors (11). One in 7 individuals diagnosed with SINT can be expected to die within 5 years (7), and elucidating lifestyle factors predisposing to this malignancy could help identify those at risk and mitigate the effects from these factors. Thus, we sought to assess the association of tobacco and alcohol exposure with SINT in a statewide cohort of patients in comparison with matched population controls.

Materials and Methods

Analysis of cancer incidence over time

SINT cancer rates were determined using the National Cancer Institute SEER Program software, SEER*Stat version 8.3.5, SEER*Stat Database (Incidence - SEER 9 Regs Research Data, Nov 2018 Sub [1975–2016] + Katrina/Rita Population Adjustment Linked to County Attributes—Total U.S., 1969–2017 Counties, National Cancer Institute, Surveillance Research Program, released April 2018, based on the November 2017 submission; available at: www.seer.cancer.gov/seerstat). Selected cancers were limited to the small-intestine site (C170-C173, C178, or C179) and a carcinoid histology (8240 or 8241). Total rates are per 100,000 and are age-adjusted to the 2000 U.S. Standard Population (19 age groups—Census P25-1130 standard). Confidence intervals (CI) are 95% for rates with Tiwari modifications and trends (13). Percentage of changes were calculated using one year for each end point; annual percentage of changes were calculated using the weighted least squares method.

Utah Population Database

The Utah Population Database (UPDB) is a shared resource located at the University of Utah that consists of computerized data records for over 11 million people who either currently reside in Utah or who formerly lived in the state (www.uofuhealth.utah.edu/huntsman/utah-population-database/data/). To be included in the database, an individual must have one or more record-based events within Utah from the late 1800s to the current day. These records, currently numbering approximately 35 million, include: U.S. Census of Utah (1880–1940); Utah births, marriages, and deaths (from 1904); voter registrations and driver license renewals (from the 1970s); cancers in the Utah Cancer Registry (UCR), a SEER registry that has collected all cancers diagnosed in Utah from 1966; or an administrative claims record in a statewide file of inpatient and ambulatory facility discharges from 1996 provided by the Utah Department of Health (UDOH). These data are updated at least annually, and probabilistic record-linking is performed with individuals in UPDB as described previously (14). In addition, the UPDB contains links to clinical records of millions of patients in the University of Utah Health (UHealth) and Intermountain Healthcare (IH) systems which account for approximately 85% of patient encounters in Utah annually. These electronic medical records (EMR) from 1996 include International Classification of Diseases, 9th and 10th version (ICD-9 and ICD-10) diagnosis codes. A unique feature of the database is an extensive genealogy of several generations of family relationships that are updated on an ongoing basis as individuals are linked to pedigrees based on vital records and other information. It is the only database of its kind in the United States, and one of a few in the world; most families living in Utah are represented in the UPDB.

This study was conducted in accordance with the Declaration of Helsinki and the U.S. Federal Policy for the Protection of Human Subjects (Common Rule). Approvals were granted and waivers of consent obtained to conduct this records-based study from the University of Utah Institutional Review Board, Intermountain

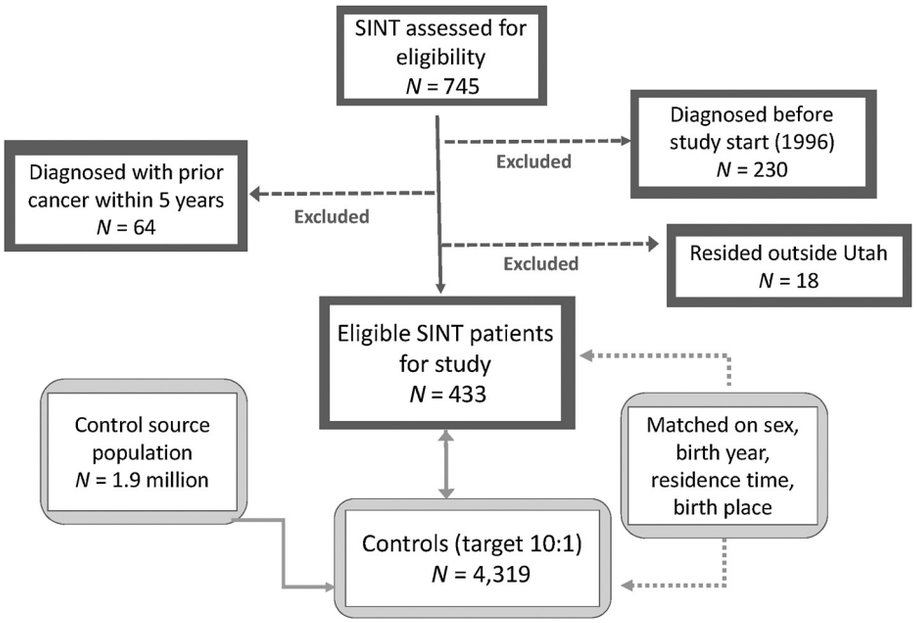

Figure 2.
Small-intestine neuroendocrine tumor (SINT) case and control selection.

Healthcare Research Institutional Review Board, and by the body governing research use of UPDB data, the Utah Resource for Genetic and Epidemiologic Research.

Case and control subjects

Adult cases ages 18 and older were identified as follows: A diagnosis of SINT in a UCR record based on International Classification of Diseases for Oncology (ICD-O-3) site codes C170-C173, C178, or C179 and a histology code of 8240 ($N = 739$) or 8241 ($N = 6$). Of 745 SINT cases diagnosed in Utah available for analysis, we excluded: (i) those who were diagnosed before January 1, 1996, before when comprehensive tobacco and alcohol exposure data became available ($N = 230$); (ii) cases who were diagnosed with a prior cancer within 5 years of a SINT diagnosis, to minimize selection bias from an incidental finding related to a metachronous cancer ($N = 64$); and, (iii) those who resided outside of Utah for whom appropriate matched controls were not available ($N = 18$), resulting in 433 SINT for analysis (Fig. 2). Of a source population of 1.9 million individuals ages 18 and older living in Utah based on the 2010 U.S.-Utah Census, we randomly selected 4,319 individually matched controls (target control to case ratio, 10:1; actual ratio, 9:97:1) for study. Population controls who had no diagnosis history of SINT were individually matched to cases based on: family relationships available in UPDB or no pedigree information, born in Utah or outside of Utah, sex, birth year, and residence time (years) in Utah up to the year in which their respective case was diagnosed. Controls also had to be living in Utah at the time of diagnosis of their respective case (Fig. 2).

Tobacco and alcohol exposures

We assessed ever- or never-exposed to tobacco and alcohol before the date of SINT diagnosis (for controls, the diagnosis date of their respective, matched case) from International Classification of Diseases 9th or 10th Revision (ICD-9, ICD-10) codes (Supplementary Table S1), appearing in any diagnostic position, in one or more statewide UDOH and UHealth/IH electronic medical records from 1996. It has been previously shown that ICD-9 tobacco use codes can identify smokers in a clinical population (15). We also had access to a limited set of self-reported tobacco and alcohol histories (including self-reported never use) taken routinely at each inpatient or outpatient encounter in a UHealth facility from 2009 for 98 cases and 752 controls (23% and 18% of cases and controls, respectively) to provide corroboration of prior tobacco and alcohol exposure from ICD codes, and to explore intensity and duration of exposure in a limited subset.

Statistical analyses

Multivariate conditional logistic regression was used to provide an odds ratio (OR) estimate of the risk of SINT given the tobacco- and alcohol-exposure status of case subjects compared with control subjects. Models accounting for individual matching variables of sex, birth year, born in or outside of Utah, and availability of family relationships in UPDB (yes/no) were further adjusted for race (Caucasian/not Caucasian) and ethnicity (Hispanic or not Hispanic), and family history of a carcinoid tumor (in any first- or second-degree relative), as we have reported a significant familial risk of SINT in relatives of patients with SINT (9). Differential effects of gender and tobacco use in relation to inflammatory bowel disease have also been reported (16). Thus, we also examined sex- and family-history stratified models as planned analyses.

Results

We observed a steady increase of the annual percentage of change in SINT incidence per 100,000 from 1975 to 2016 of 2.50% (95% CI, 2.13–2.86; $P < 0.05$) using national SEER data (Fig. 1), which translates to a 3.2-fold increase over this 41-year period. We found that Utah SEER data have paralleled the national trend, while reflecting a higher SINT incidence in most years and a consistent increase in age-adjusted annual percent change of 2.43% per year (95% CI, 1.69%–3.17%; $P < 0.05$).

Table 1. Characteristics of small-intestine neuroendocrine tumor (SINT) study subjects

	10:1 controls		SINT patients		
Characteristic	***N***	**col%**	***N***	**col%**	***P*[a]**
Total	4,319	100.0	433	100.0	
Men	2,442	56.5	245	56.6	
Women	1,877	43.5	188	43.4	0.99
Birthplace					
Utah	2,332	54.0	235	54.3	
Outside of Utah	1,987	46.0	198	45.7	0.91
Family relationships in UPDB					
Yes	4,173	96.6	420	97.0	
No	146	3.4	13	3.0	0.68
Age at case diagnosis					
26 to 50 y	962	22.3	100	23.1	
51 to 64 y	1,377	31.9	139	32.1	
65 to 90 y	1,980	45.8	194	44.8	0.90
Race					
Caucasian	4,213	97.5	419	96.8	
Non-Caucasian/mixed race	106	2.5	14	3.2	0.33
Ethnicity					
Hispanic	258	6.0	24	5.5	
Non-Hispanic	4,061	94.0	409	94.5	0.72
Family history of carcinoid tumors					
Absent	4,287	99.3	417	96.3	
Present	32	0.7	16	3.7	<0.0001
Vital status, December 31, 2017					
Alive	3,366	77.9	268	61.9	
Deceased	953	22.1	165	38.1	<0.0001
Tobacco use					
Exposed	693	16.0	92	21.2	
Unexposed	3,626	84.0	341	78.8	0.006
Tobacco use in men					
Exposed	448	18.3	57	23.3	
Unexposed	1,994	81.7	188	76.7	0.06
Tobacco use in women					
Exposed	245	13.1	35	18.6	
Unexposed	1,632	86.9	153	81.4	0.03
Alcohol use					
Exposed	170	3.9	27	6.2	
Unexposed	4,149	96.1	406	93.8	0.02
Alcohol use in men					
Exposed	111	4.5	16	6.5	
Unexposed	2,331	95.5	229	93.5	0.16
Alcohol use in women					
Exposed	59	3.1	11	5.9	
Unexposed	1,818	96.9	177	94.1	0.05

Abbreviations: SINT, small-intestine neuroendocrine tumor; y, years.
[a]The χ^2 test.

Table 2. Characteristics of small-intestine neuroendocrine tumors in patients with SINT

			Tobacco use				
	Total		Unexposed		Exposed		
Tumor characteristic	***N***	**col%**	***N***	**col%**	**N**	**col%**	***P*[a]**
SINT patients	433	100.0	341	100.0	92	100.0	
SEER summary stage							
Local	162	37.4	127	37.2	35	38.0	
Regional	182	42.0	141	41.3	41	44.6	
Distant	81	18.7	66	19.4	15	16.3	
Not available	8	1.9	7	2.1	*	1.1	0.88
Grade							
Well differentiated	134	30.9	99	29.0	35	38.0	
Moderately differentiated	41	9.5	30	8.8	11	12.0	
Poorly differentiated	*	0.5	*	0.6	0	0.0	
Not available	256	59.1	210	61.6	46	50.0	0.18

NOTE: An asterisk (*) was used to mask cell counts of $N < 5$.
Abbreviations: SEER, Surveillance, Epidemiology, and End Results Program; SINT, small-intestine neuroendocrine tumor.
[a]Fisher's exact test.

Descriptive characteristics of study subjects are shown in Table 1. More men than women were diagnosed with SINT (56.6% vs. 43.4%, respectively), and more than half were diagnosed before age 65 (55.2%). A majority of cases and controls had family relationships available in UPDB genealogy records to assess SINT family history (97%). Most participants were non-Hispanic Caucasians, and race/ethnicity did not differ between SINT cases and controls. The number of cases with a family history of SINT (3.7%) was higher than that of controls (0.7%) as expected, and cases were more likely to have died on or before December 31, 2017. Tobacco use (ever exposed) before case diagnosis was indicated in 21.2% of SINT cases compared with 16.0% of controls, a statistically significant difference ($P = 0.006$, χ^2 test; see Table 1). A higher rate of alcohol use (ever exposed) was also observed in cases. The characteristics of tumors in patients with SINT are shown in Table 2, overall and by tobacco exposure status. Most patients had SEER summary stage information available (98.2%) while tumor grade was only available in less than half of SINT cases. Overall, of 425 SINT in which stage was available, 38.1% were local and 42.8% were regional stage. Distant metastases were present in 19.1% of cases. In 177 cases with available grade information, most had a low-grade, well-differentiated tumor (75.7%) or moderately differentiated tumor (23.2%) whereas only two cases had a high-grade tumor. These tumor characteristics did not differ between those unexposed and those exposed to tobacco (Table 2, Fisher's exact test).

OR risk estimates and 95% CIs for risk of ever exposed to tobacco and alcohol compared with unexposed are shown in Fig. 3. Overall, ever-exposed to tobacco primarily from cigarette smoking suggested a modest 1.4-fold increased risk of SINT (OR, 1.44; 95% CI, 1.11–1.86; $P = 0.006$; Fig. 3A). When restricted to cases and their individually matched controls who had no family history of SINT, tobacco exposure was associated with a similar increased risk of SINT (OR, 1.47; 95% CI, 1.13–1.90; $P = 0.004$; Fig. 3B). Exposure to tobacco and risk of SINT was somewhat more pronounced in women than in men, although confidence intervals overlapped. On the basis of a limited subset of subjects with self-reported tobacco exposure, including duration and intensity, patients with SINT and controls did not differ in years since quit smoking nor in years smoked. However, the proportion of SINT cases who reported smoking >1 pack per day was significantly higher (Supplementary Table S2). Of model covariates, a family history of SINT was the strongest independent predictor of an individual's SINT risk ($P < 0.0001$). Race and ethnicity were not significantly associated.

In regard to prior exposure to alcohol, an overall 1.6-fold risk of SINT was observed (OR, 1.62; 95% CI, 1.05–2.49; $P = 0.03$; Fig. 3A) that was similar in subjects with no SINT family history (OR, 1.58; 95% CI, 1.01–2.46; $P = 0.04$; Fig. 3B). When prior history of alcohol use was examined in men and women separately, women exposed to ever use of alcohol had a somewhat more pronounced risk of SINT overall than did men, however confidence intervals overlapped and a difference by sex was not significant (Fig. 3).

Discussion

Our findings are consistent with other reports of an association between exposure to tobacco, primarily from smoking cigarettes,

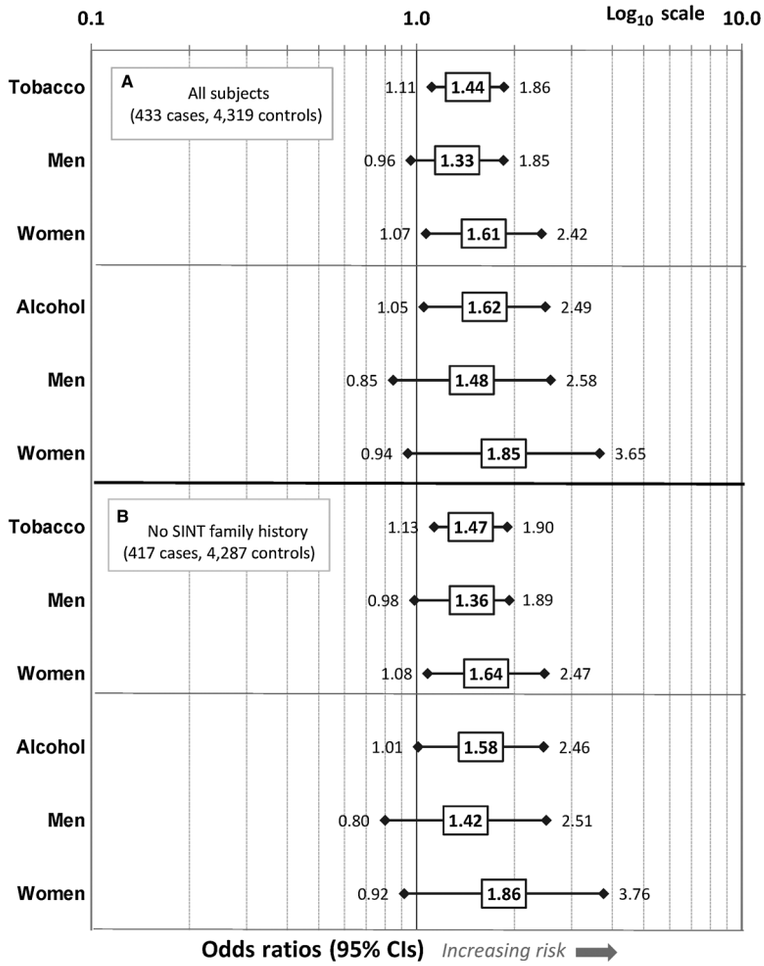

Figure 3.
Ever exposed to tobacco or alcohol and risk of SINT compared with 10:1 controls, overall and for men and women separately. **A,** Odds ratios and 95% confidence intervals for all subjects are shown. **B,** Estimates represent subjects without a family history of SINT.

and risk of SINT. The point estimate we observed of an approximately 1.4-fold risk for history of ever smoking in our statewide population study was consistent with a 1.4- to 1.6-fold summary OR reported in meta-analyses of a limited number of studies (10, 11). Because individual records are linked with family history and statewide cancers, we were able to exclude those with a SINT family history and found a similar association between exposure to tobacco and risk of SINT. We acknowledge the possibility that exposed subjects, particularly tobacco users, may have related comorbidities leading to increased testing and incidental detection of SINT and some of the increase we observed in tobacco-exposed patients could be due to incidental findings. To minimize possible selection bias due to incidental findings, we excluded patients diagnosed with a prior cancer within 5 years of a SINT diagnosis. Furthermore, the rates of tobacco and alcohol exposures did not differ in patients with SINT for earlier- or later-stage disease.

We observed an association with prior alcohol use and SINT overall and in women, and an association of similar magnitude in men that was of borderline significance only ($P = 0.09$). Studies have found links between alcohol and colorectal cancer in both men and women; however, the evidence is generally stronger in men (www.cancer.org/cancer/cancer-causes/diet-physical-activity/alcohol-use-and-cancer.html). Findings within three previous studies analyzed for ever-alcohol consumption and risk of SINT were inconsistent, and a summary estimate was not significant. Further studies are important to provide confirmation of an association with exposure to alcohol, or lack there-of (10, 11). The strongest risk factor for SINT in our study was having a family history of carcinoid cancer which conferred 5-fold increased risk independent of tobacco and alcohol exposure. This is not surprising, given the familial nature of SINT has been established.

We note the ability of our study to accurately assess exposures to tobacco and alcohol in this large-population study was limited, and we acknowledge misclassification bias may have occurred. According to the Centers for Disease Control and Prevention (CDC) Behavioral Risk Factor Surveillance System (BRFSS), the estimated percentage of Utah adults who were currently smoking cigarettes in 1995 (the year before the start of our study) was 13.2% (16.4% of men and 10.0% of women; see BRFSS Prevalence and Trends Data, available at: www.cdc.gov/brfss/brfssprevalence/). The percentage of control subjects in our study with an indication of tobacco use was slightly higher than that of the CDC estimate. However, our study includes both current and quit smokers. In the subset of 98 SINT and 752 control subjects who provided self-reported tobacco use histories, quit smokers outnumbered current smokers (see Supplementary Table S2). If restricted to an indication of current use only, our study prevalence is comparable with the estimated population prevalence of current smoking. Indication of alcohol exposure from ICD abuse

and dependence codes likely did not capture moderate or occasional drinkers. The estimated prevalence of persons in Utah who reported heavy drinking (>2 alcoholic drinks/day for men and >1 drink/day for women during the preceding month) was 3.7% based on the BRFSS 2015 survey (BRFSS Prevalence and Trends Data, available at: www.cdc.gov/brfss/brfssprevalence/), similar to that observed in our study controls (3.9%). In the subset of 85 SINT and 496 control subjects with self-reported alcohol use histories, a somewhat higher percentage reported current consumption of alcohol, 5.2% and 7.1%, respectively; however, few subjects reported heavy consumption of >14 gm of alcohol per week (Supplementary Table S2).

We believe that misclassification of never-exposed individuals in our study was limited, as Utah has the lowest smoking and alcohol consumption rates in the United States due to religious proscriptions against drinking and smoking (17, 18). Conversely, Utah has experienced higher historic and current incidence of SINT than in other regions (Fig. 1). The age-adjusted incidence rate of SINT in Utah from 2001 to 2016 was 1.5 per 100,000, the highest rate among 21 different SEER registries. In 2016, Utah had the third-highest rate, 1.7, behind Iowa and Atlanta (SEER*Stat Database: Incidence—SEER 21 Regs Limited-Field Research Data + Hurricane Katrina Impacted Louisiana Cases, Nov 2018 Sub (2000–2016)—Linked To County Attributes—Total U.S., 1969–2017 Counties, available at: www.seer.cancer.gov/seerstat). Increasing incidence of SINT in Utah and elsewhere may be due, at least in part, to increased detection of earlier-stage tumors. In our data, the median diagnosis year for distant stage SINT occurred 2 years earlier than that for non-distant metastases. However, our findings of an association with tobacco and alcohol exposure suggest that these factors may also be contributing to SINT in Utah.

In conclusion, our study of a statewide population supports an association of tobacco use with a modest increased risk of SINT, independent of family history, consistent with previous reports. Our findings suggest that alcohol use may also be associated with a modest increased SINT risk. However, relatively low rates of tobacco and alcohol use coupled with higher rates of SINT in Utah suggest other exogenous or endogenous factors and increased diagnosis may be contributing to development of these tumors.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

Authors' Contributions

Conception and design: K. Curtin, J. VanDerslice, D.W. Neklason
Development of methodology: K. Curtin
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): K. Curtin, L.A. Cannon-Albright, Z. Yu, K.A. Herget, D.W. Neklason
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): K. Curtin, J. VanDerslice, Z. Yu, K.A. Herget, D.W. Neklason
Writing, review, and/or revision of the manuscript: K. Curtin, L.A. Cannon-Albright, J. VanDerslice, K.A. Herget, R. Thota, D.W. Neklason
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): K. Curtin, R. Thota
Study supervision: K. Curtin, D.W. Neklason

Acknowledgments

Research reported in this publication was supported by the National Institutes of Health (NIH) National Cancer Institute grants R21 CA205796 (D. Neklason, PI) and Cancer Center Support Grant P30 CA42014 (C. Ulrich, PI). The Utah Cancer Registry is funded by the National Cancer Institute's SEER Program, Contract No. HHSN261201800016I (J. Doherty, PI), and the U.S. Center for Disease Control and Prevention's National Program of Cancer Registries, Cooperative Agreement No. NU58DP0063200. Research was supported by a National Center for Research Resources grant, "Sharing Statewide Health Data for Genetic Research" (R01 RR021746, G. Mineau, PI) with additional support from the Utah State Department of Health, the University of Utah, and Huntsman Cancer Foundation. The authors thank the University of Utah Center for Clinical and Translational Science, funded by an NIH Clinical and Translational Science Award UL1TR002538 (W. Dere, PI; formerly 5UL1TR001067-05, 8UL1TR000105, and UL1RR025764), the Pedigree and Population Resource, and the University of Utah Information Technology Services and Biomedical Informatics Core for establishing the Master Subject Index between the Utah Population Database, the University of Utah Health Sciences Center and Intermountain Health Care. The authors also acknowledge the Utah Population Database for the resources provided to this study.

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Received May 18, 2019; revised August 12, 2019; accepted September 17, 2019; published first September 26, 2019.

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