Published in final edited form as:

Cancer Epidemiol Biomarkers Prev. 2019 December ; 28(12): 1998–2004. doi:
10.1158/1055-9965.EPI-19-0465.

Associations of tobacco and alcohol use with risk of neuroendocrine tumors of the small intestine in Utah

Karen Curtin^{1,2}, Lisa A. Cannon-Albright^{1,2,4}, James VanDerslice³, Zhe Yu², Kimberly A. Herget⁵, Ramya Thota⁶, Deborah W. Neklason^{1,2}

¹Division of Epidemiology, Department of Internal Medicine, University of Utah, Salt Lake City, Utah

²Huntsman Cancer Institute, University of Utah, Salt Lake City, Utah

³Division of Public Health, Department of Family and Preventive Medicine, University of Utah, Salt Lake City, Utah

⁴George E. Wahlen Department of Veterans Affairs Medical Center, Salt Lake City, Utah

⁵Utah Cancer Registry, University of Utah, Salt Lake City, Utah

⁶Hematology/Oncology, Intermountain Healthcare, Salt Lake City, Utah

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 in 1996–2014 with no prior history of cancer within 5 years ($n=433$) were matched to population controls (1:10 ratio). Tobacco and alcohol exposures prior to 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% $CI=1.11-1.86$, $p=0.006$). 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: While 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.

Correspondence: Karen Curtin, PhD, Huntsman Cancer Institute at the University of Utah, 2050 Circle of Hope, Salt Lake City, UT, 84112, Phone 1-801-585-5320, karen.curtin@hsc.utah.edu.

The authors declare no potential conflicts of interest.

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 (Figure 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 SINT patients, 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 et al. reported a summary estimate of a significant 1.6-fold increased risk of SINT in ever vs. never smokers based on two case-control studies in the U.S. and one in Europe (10), while Haugvik, et al. reported a similar 1.4-fold risk of SINT in ever-smokers based on three U.S. and two European populations (11). With regard to alcohol consumption, a meta-association of ever vs. 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 et al. reported that smoking conferred a significant 1.5-fold risk for small-intestine carcinoid cancer which in heavy smokers was higher, 1.9-fold (12). 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.

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). Percent changes were calculated using one year for each end point; annual percent 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 ~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 (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 which 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 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: 1) those who were diagnosed before January 1, 1996, prior to when comprehensive tobacco and alcohol exposure data became available (N=230); 2) 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, 3) those who resided outside of Utah for whom appropriate matched controls were not available (N=18), resulting in 433 SINT for analysis (Figure 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 4319 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 (Figure 2).

Tobacco and alcohol exposures.

We assessed ever- or never-exposed to tobacco and alcohol prior to 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 (Supplemental 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 SINT patients (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 percent 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 (Figure 1), which translates to a 3.2-fold increase over this 41-year period. We found that Utah SEER data has 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%; $p<0.05$).

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) prior to case diagnosis was indicated in 21.2% of SINT cases compared with 16.0% of controls, a statistically significant difference ($p=0.006$, chi-square test; see Table 1). A higher rate of alcohol use (ever exposed) was also observed in cases. The characteristics of tumors in SINT patients 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%) while 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).

Odds ratio (OR) risk estimates and 95% CIs for risk of ever exposed to tobacco and alcohol compared with unexposed are shown in Figure 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, $p=0.006$; Figure 3, Panel 3.a). 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, $p=0.004$; Figure 3, Panel 3.b.). Exposure to tobacco and risk of SINT was somewhat more pronounced in women than in men, although confidence intervals overlapped. Based on a limited subset of subjects with self-reported tobacco exposure including duration and intensity, SINT patients 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 (Supplemental 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, $p=0.03$; Figure 3, Panel 3.a.) that was similar in subjects with

no SINT family history (OR=1.58, 95%CI=1.01-2.46, $p=0.04$; Figure 3, Panel 3.b.). 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 (Figure 3).

Discussion

Our findings are consistent with other reports of an association between exposure to tobacco, primarily from smoking cigarettes, and risk of SINT. The point estimate we observed of a ~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 odds ratio 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. In order 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 SINT patients 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 prior to the start of our study) was 13.2% (16.4% of men and 10.0% of women (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 Supplemental Table S2). If restricted to an indication of current use only, our study prevalence is comparable to 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 >14gm of alcohol per week (Supplemental 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 (Figure 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 two years earlier than that for non-distant metastases. However, our findings of an association with tobacco and alcohol exposure suggests 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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. HHSN2612018000161 (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. We 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. We also acknowledge the Utah Population Database for the resources provided to this study. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

Abbreviations:

SINT	small intestine neuroendocrine tumor
UPDB	Utah Population Database
OR	odds ratio
CI	confidence interval

References

1. Delle Fave G, Capurso G, Milione M, Panzuto F. Endocrine tumours of the stomach. *Best Pract Res Clin Gastroenterol* 2005;19(5):659–73 doi 10.1016/j.bpg.2005.05.002. [PubMed: 16253892]
2. Kharazmi E, Pukkala E, Sundquist K, Hemminki K. Familial risk of small intestinal carcinoid and adenocarcinoma. *Clin Gastroenterol Hepatol* 2013;11(8):944–9 doi 10.1016/j.cgh.2013.02.025. [PubMed: 23500615]
3. DiSario JA, Burt RW, Vargas H, McWhorter WP. Small bowel cancer: epidemiological and clinical characteristics from a population-based registry. *Am J Gastroenterol* 1994;89(5):699–701. [PubMed: 8172140]
4. Neugut AI, Jacobson JS, Suh S, Mukherjee R, Arber N. The epidemiology of cancer of the small bowel. *Cancer Epidemiol Biomarkers Prev* 1998;7(3):243–51. [PubMed: 9521441]
5. Modlin IM, Kidd M, Lye KD. Biology and management of gastric carcinoid tumours: a review. *Eur J Surg* 2002;168(12):669–83. [PubMed: 15362575]
6. Yao JC, Hassan M, Phan A, Dagohoy C, Leary C, Mares JE, et al. One hundred years after “carcinoid”: epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. *J Clin Oncol* 2008;26(18):3063–72 doi 10.1200/JCO.2007.15.4377. [PubMed: 18565894]
7. Tsikitis VL, Wertheim BC, Guerrero MA. Trends of incidence and survival of gastrointestinal neuroendocrine tumors in the United States: a seer analysis. *J Cancer* 2012;3:292–302 doi 10.7150/jca.4502. [PubMed: 22773933]
8. Dasari A, Shen C, Halperin D, Zhao B, Zhou S, Xu Y, et al. Trends in the Incidence, Prevalence, and Survival Outcomes in Patients With Neuroendocrine Tumors in the United States. *JAMA Oncol* 2017;3(10):1335–42 doi 10.1001/jamaoncol.2017.0589. [PubMed: 28448665]
9. Neklason DW, VanDerslice J, Curtin K, Cannon-Albright LA. Evidence for a heritable contribution to neuroendocrine tumors of the small intestine. *Endocr Relat Cancer* 2016;23(2):93–100 doi 10.1530/ERC-15-0442. [PubMed: 26604321]
10. Leoncini E, Carioli G, La Vecchia C, Boccia S, Rindi G. Risk factors for neuroendocrine neoplasms: a systematic review and meta-analysis. *Ann Oncol* 2016;27(1):68–81 doi 10.1093/annonc/mdv505. [PubMed: 26487581]
11. Haugvik SP, Basim Ibrahim I, Hedenstrom P, Valente R, Hayes AJ, Siuka D, et al. Smoking, alcohol and family history of cancer as risk factors for small intestinal neuroendocrine tumors: a systematic review and meta-analysis. *Scand J Gastroenterol* 2017;52(8):797–802 doi 10.1080/00365521.2017.1310290. [PubMed: 28394712]
12. Rinzivillo M, Capurso G, Campana D, Fazio N, Panzuto F, Spada F, et al. Risk and Protective Factors for Small Intestine Neuroendocrine Tumors: A Prospective Case-Control Study. *Neuroendocrinology* 2016;103(5):531–7 doi 10.1159/000440884. [PubMed: 26356731]
13. Tiwari RC, Clegg LX, Zou Z. Efficient interval estimation for age-adjusted cancer rates. *Stat Methods Med Res* 2006;15(6):547–69 doi 10.1177/0962280206070621. [PubMed: 17260923]

14. Prahalad S, Zeft AS, Pimentel R, Clifford B, McNally B, Mineau GP, et al. Quantification of the familial contribution to juvenile idiopathic arthritis. *Arthritis Rheum* 2010;62(8):2525–9 doi 10.1002/art.27516. [PubMed: 20506132]
15. Wiley LK, Shah A, Xu H, Bush WS. ICD-9 tobacco use codes are effective identifiers of smoking status. *J Am Med Inform Assoc* 2013;20(4):652–8 doi 10.1136/amiajnl-2012-001557[pil]. [PubMed: 23396545]
16. Parkes GC, Whelan K, Lindsay JO. Smoking in inflammatory bowel disease: impact on disease course and insights into the aetiology of its effect. *J Crohns Colitis* 2014;8(8):717–25 doi 10.1016/j.crohns.2014.02.002. [PubMed: 24636140]
17. Merrill RM, Lyon JL. Cancer incidence among Mormons and non-Mormons in Utah (United States) 1995-1999. *Prev Med* 2005;40(5):535–41 doi 10.1016/j.ypmed.2004.10.011. [PubMed: 15749135]
18. Pickens CM, Pierannunzi C, Garvin W, Town M. Surveillance for Certain Health Behaviors and Conditions Among States and Selected Local Areas - Behavioral Risk Factor Surveillance System, United States, 2015. *MMWR Surveill Summ* 2018;67(9):1–90 doi 10.15585/mmwr.ss6709a1.

Figure 1.

Cases of SINT per 100,000 population in 1975-2016 in Utah compared with other SEER registries. Rates are age-adjusted to the 2000 U.S. Standard Population standard using Surveillance Research Program, National Cancer Institute SEER*Stat software version 8.3.5 (www.seer.cancer.gov/seerstat). SEER 9 data is 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.

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

Figure 3.

Ever exposed to tobacco or alcohol and risk of small intestine neuroendocrine tumor (SINT) compared with 10:1 controls, overall and for men and women separately. In Panel 3.a., odds ratios and 95% confidence intervals for all subjects are shown. In Panel 3.b., estimates represent subjects without a family history of SINT.

Table 1.

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

Characteristic	10:1 controls		SINT patients		<i>p</i> ^a
	N	col%	N	col%	
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

Characteristic	10:1 controls		SINT patients		<i>p</i> ^a
	N	col%	N	col%	
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 endocrine tumor; y, years.

^aChi-square test.

Table 2.

Characteristics of small intestine neuroendocrine tumors in SINT patients.

	Total		Tobacco use				<i>p</i> ^a
			Unexposed		Exposed		
Tumor characteristic	N	col%	N	col%	N	col%	
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

Abbreviations: SINT, small intestine neuroendocrine tumor; SEER, Surveillance, Epidemiology, and End Results Program.

Note: an asterisk (*) was used to mask cell counts of N <5.

^aFisher's exact test.