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A large prospective study of risk factors for adenocarcinomas and malignant carcinoid tumors of the small intestine

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Abstract

Purpose—Small intestinal cancer is increasing in the U.S., yet little is known about its etiology. Our aim was to prospectively evaluate risk factors for this malignancy by the two main histologic subtypes (adenocarcinomas and carcinoids).

Methods—Hazard ratios (HRs) and 95% confidence intervals (CI) were estimated for all incident small intestinal cancers (n=237), adenocarcinomas (n=84), and malignant carcinoids (n=124), by demographic and lifestyle factors among 498,376 men and women.

Results—Age was the only risk factor for adenocarcinomas (HR for ≥ 65 vs. 50-55 years=3.12, 95% CI: 1.33, 7.31). Age (HR for ≥ 65 vs. 50-55 years=3.31, 95% CI: 1.51, 7.28), male sex (HR=1.44, 95% CI: 1.01, 2.05), body mass index (BMI, HR for ≥ 35 vs. 18.5-<25 kg/m^2=1.95, 95% CI: 1.06, 3.58), and current menopausal hormone therapy use (HR=1.94, 95% CI: 1.07, 3.50) were positively associated with malignant carcinoids. A family history of any cancer or colorectal cancer (HR=1.42, 95% CI: 0.99, 2.03; 1.61, 0.97, 2.65, respectively), or a personal history of colorectal polyps (HR=1.51, 95% CI: 0.92, 2.46) produced elevated, but not statistically significant, risks for malignant carcinoids. Race, education, diabetes, smoking, physical activity and alcohol intake were not associated with either histologic subtype.

Conclusions—Risk factors differed according to cancer subtype; only age was associated with adenocarcinomas, whereas age, male sex, BMI, and menopausal hormone therapy use were positively associated with malignant carcinoids.

Keywords

Demographic; lifestyle; risk factors; small intestine; cancer; adenocarcinoma; carcinoid

There is substantial variation in the incidence of small intestinal cancer around the world, ranging from less than 0.5 per 100,000 in some regions of Africa and Asia to 3.7 in certain areas of the U.S. [1], where incidence rates have been increasing over the last several decades [2]. Between 1975 and 2010, the annual percentage change in incidence of this malignancy in the U.S. is a statistically significant 2.4% increase [3]. Despite the global variation and increasing incidence in Western countries, little is known about small intestinal cancer. Although rare, individuals diagnosed with small intestinal cancer have a three times higher risk of developing colorectal cancer, as well as over 60% increased risk of developing any second primary cancer [4]. In the U.S., the overall five-year survival

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estimate for small intestinal cancer is 64%, and the age-adjusted mortality rate is 0.4 per 100,000 men and women per year [3]. Since the incidence of this malignancy is increasing in the U.S. and there is very little data on etiologic factors, it is imperative to investigate this malignancy in large prospective studies.

Cancer in the small intestine arises from various cell types with the two most common subtypes being adenocarcinomas, which account for approximately 30-40% of cases, and carcinoids, which account for approximately 35%-42% of cases [5-8]. The five-year survival in the U.S. is worse for adenocarcinomas (27%) than carcinoid tumors (77%) [9], although the incidence of carcinoid tumors has increased four-fold between 1973 and 2004 [10]. Risk factors may differ according to histologic subtype, but very few studies have had the ability to distinguish between these two main subtypes. The aim of this study was to prospectively investigate demographic and lifestyle risk factors for small intestinal cancer for the two main histologic subtypes in a cohort of approximately half a million men and women.

METHODS

Study population

The National Institutes of Health (NIH)-AARP Diet and Health Study is a large prospective cohort of men and women who were recruited in 1995-96 at ages 50 to 71 years from six U.S. states (California, Florida, Louisiana, New Jersey, North Carolina, and Pennsylvania) and two metropolitan areas (Atlanta, Georgia, and Detroit, Michigan); further study details have previously been described [11]. The Special Studies Institutional Review Board of the U.S. National Cancer Institute approved the study.

Exposure assessment

At recruitment, participants completed a self-administered questionnaire regarding demographic and lifestyle characteristics, which included questions on family history of cancer, and personal history of conditions such as colorectal polyps and diabetes [11]. Self-reported body weight and height were used to calculate body mass index (BMI, kg/m^2). For alcohol intake, multivitamin use, and physical activity, participants were asked to recall their usual behavior over the last twelve months. Alcohol intake included separate questions for frequency and portion size for beer (in the summer, and the rest of the year separately), wine or wine coolers, and liquor (including mixed drinks). Multivitamin use (yes/no), type of multivitamin, and frequency of use was queried. Physical activity at work or home included exercise, sports, and activities such as carrying heavy loads; vigorous physical activity was defined as activity ≥20 minutes (that increased breathing or heart rate, or worked up a sweat). The questions on smoking included whether the participants were current, former or never smokers. The current and former smokers were asked how many cigarettes they usually smoked, and former smokers were asked how long ago they quit. Smoking was defined as never, quit ≥ 10 years ago, quit 1 to 9 years ago, current smoker (includes those who quit within the last 12 months) smoking ≤ 20 cigarettes per day, and current smoker smoking >20 cigarettes per day. These smoking categories were sufficiently detailed whilst retaining an adequate number of cases in each exposure category. The questionnaire also assessed the use and duration (never, less than 5 years, 5 to 9 years, or 10 or more years) of menopausal hormone therapy use among women.

Cohort follow-up and case ascertainment

Participants were followed by annual matching of the cohort with the National Change of Address database maintained by the U.S. Postal Service and through processing of undeliverable mail, other address update services, and direct responses from participants. Vital status was determined by annual linkage of the cohort to the U.S. Social Security

Administration Death Master File, searches of the National Death Index Plus, linkage to state cancer registries, questionnaire responses, and responses to other mailings. Follow-up for these analyses began on the date the questionnaire was received until censoring at the end of 2006, or when the participant moved out of one of the state cancer registry areas (which included the eight states participants were recruited from plus Texas and Arizona where participants commonly move to), had a cancer diagnosis, or died, whichever came first.

Cancer cases were ascertained through probabilistic linkage with state cancer registries using first and last names, sex, date of birth, and social security number provided on the baseline questionnaire, and address history. The state cancer registries are certified by the North American Association of Central Cancer Registries as being at least 90% complete within two years of cancer occurrence. The case ascertainment method used in our study was estimated to identify approximately 90% of all cancer cases in our cohort [12]. For these analyses, cancer cases were first primary registry-confirmed malignant cancers of the small intestine defined by anatomic site and histologic code of the International Classification of Diseases for Oncology (ICD-O-3) [13] codes C170-C179, ICD-9 code 152 (which includes codes 152.0, 152.1, 152.2, 152.3, 152.8, 152.9). Furthermore, using the data provided by the cancer registries, we analyzed our data according to the two main histologic subtypes of adenocarcinomas (ICD-O-3 morphology codes: 8140, 8145, 8210, 8261, 8263, 8480, 8481, 8490 from cases diagnosed within our cohort) and carcinoid tumors (ICD-O-3 morphology codes: 8156, 8240, 8241, 8246, 8249).

Statistical analysis

After excluding duplicates and participants who died or moved before the questionnaire was received or withdrew from the study, a total of 566,401 participants returned the baseline questionnaire. Individuals were excluded if their questionnaire was filled in by someone else on their behalf (n = 15,760), they had prevalent cancer according to the cancer registry or self-report (n = 51,216), they had end-stage renal disease (n = 997), or they had zero person years of follow-up as a result of dying before the baseline questionnaire was scanned in by the study centre (n = 7). After all exclusions, this analytic cohort included 498,376 persons (297,250 men and 201,126 women).

We calculated age standardized incidence rates of small intestinal cancer by histologic subtype within the NIH-AARP Diet and Health Study per 100,000 person-years for both men and women. Cox proportional hazards regression was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) using age as the underlying time metric. The proportional hazards assumption was verified using a time interaction model. Since very little is known about the risk factors for this malignancy, the models were adjusted for age, follow-up time, and sex. Separate indicator variables were included in the models for exposures with missing values; for any one exposure this ‘missing’ category included 5% or less of the cohort. We investigated interactions by gender by including cross product terms. Tests for linear trends across exposures were calculated by treating the categorical variables as ordinal variables. Global *P*-values were calculated for race using the Chi squared test with the appropriate degrees of freedom. Finally, we conducted a lag analysis, excluding cases diagnosed within the first year of follow-up. *P*-values are two-sided and all statistical analyses were carried out using Statistical Analysis Systems (SAS) software (SAS Institute Inc, Cary, NC).

RESULTS

During a median follow-up time of 10.5 years, a total of 237 small intestinal cancers were diagnosed (147 in men, and 90 in women). The cases comprised of 84 adenocarcinomas (59

male and 25 female) and 124 malignant carcinoid tumors (70 male and 54 female); the remaining 29 cases were histologically not otherwise specified (NOS, n = 6), sarcomas (n = 21), mesothelioma (n = 1), and an adenocarcinoid (n = 1). Regarding sub-sites within the small intestine, 73 cases had duodenal cancers, 24 had jejunal cancers, 70 had ileal cancers, and the exact site of the remaining 70 could not be determined. Adenocarcinomas occurred most frequently in the duodenum (63% of all duodenal cancers were adenocarcinomas, 26% malignant carcinoids, 5% sarcomas, 5% NOS) and jejunum (50% were adenocarcinomas, 25% malignant carcinoids, 21% sarcomas, and 4% NOS). Malignant carcinoid tumors were mainly located in the ileum (79% of ileal cancers were malignant carcinoids, 14% adenocarcinomas, 4% sarcomas, 1% adenocarcinoid, and 1% NOS). We did not observe an increasing number of diagnoses by calendar time.

The age standardized incidence rates for small intestinal cancer in our cohort were 5.5 and 4.8 per 100,000 person-years for men and women, respectively. For the histologic subtypes, the incidence rates per 100,000 person-years in our cohort were 2.2 and 1.3 for adenocarcinomas, and 2.6 and 2.9 for carcinoids, for men and women, respectively.

The percentage of current smokers was lower for those with an adenocarcinoma (10.2% in men, and 16.0% in women) or a malignant carcinoid tumor (5.7% in men, and 11.1% in women) of the small intestine compared to the percentage of current smokers in the whole cohort (12.2% of men, and 16.2% of women, Table 1); this was the only variable examined that showed a similar trend in men and women across both histologic subtypes. Other characteristics differed according to histologic subtype supporting the need to examine these tumors separately. Individuals with malignant carcinoid tumors of the small intestine were more likely to be non-Hispanic white (96% of men and 94% of women with carcinoids were non-Hispanic white, compared to 92% of men and 89% of women in the cohort overall), whereas women with an adenocarcinoma were more likely to be non-Hispanic black (12.0% compared to 5.8% of women in the cohort overall, Table 1). Individuals with malignant carcinoid tumors were more likely to have a positive family history of cancer (any or colorectal cancer), and have a personal history of colorectal polyps, and women with a malignant carcinoid tumor were more likely to be current users of menopausal hormone therapy. In contrast, those with an adenocarcinoma were less physically active and consumed more alcohol than the cohort overall (Table 1).

Age at baseline was a risk factor for all small intestinal cancers (HR for those aged ≥ 65 years versus 50-<55 years=3.39, 95% CI: 1.94, 5.91, *P-trend* <0.0001); this positive association was observed for both histologic subtypes (HR for adenocarcinomas=3.12, 95% CI: 1.33, 7.31, *P-trend*=0.0007; HR for malignant carcinoid tumors=3.31, 95% CI: 1.51, 7.28, *P-trend*=0.0006) (Table 2). Other than age, none of the other demographic factors examined were associated with adenocarcinoma of the small intestine (Table 2).

We found that men had an elevated risk of carcinoid tumors compared to women (HR=1.44, 95% CI: 1.01, 2.05). We also observed a borderline significant elevated risk for malignant carcinoid tumors in the small intestine among individuals with a positive family history of any cancer (HR=1.42, 95% CI: 0.99, 2.03), family history of colorectal cancer specifically (HR=1.61, 95% CI: 0.97, 2.65), or personal history of colorectal polyps (HR=1.51, 95% CI: 0.92, 2.46; Table 2). We did not observe any associations between other demographic factors and malignant carcinoids of the small intestine, including race, education, or diabetes (Table 2).

There were no associations between any of the lifestyle variables we investigated and adenocarcinoma of the small intestine (Table 3). For malignant carcinoid tumors of the small intestine, however, we observed an increased risk among individuals with a BMI ≥35

kg/m^2, compared to those with a BMI of 18.5 to <25 kg/m^2 (HR=1.95, 95% CI: 1.06, 3.58, *P-trend*=0.025; Table 3). Furthermore, compared to women who had never used menopausal hormones, women who previously took or were currently taking menopausal hormones had an elevated risk of malignant carcinoid tumors (HR=2.29, 95% CI: 1.00, 5.24; HR=1.94, 95% CI: 1.07, 3.50 for former and current use, respectively). We did not observe any associations between other modifiable risk factors in relation to malignant carcinoid tumors of the small intestine, including smoking, physical activity, alcohol intake (total or the subgroups of wine, beer, or liquor), or multivitamin use (Table 3).

A lag analysis excluding the cases diagnosed within the first year of follow-up did not meaningfully alter any of the associations we observed. Furthermore, stratification by sex did not reveal any other associations, and the associations observed were consistent across men and women.

DISCUSSION

We conducted a large prospective study of demographic and lifestyle factors in relation to adenocarcinomas and malignant carcinoid tumors of the small intestine. Only age at baseline was positively associated with adenocarcinoma of the small intestine, whereas male sex, age at baseline, BMI, and menopausal hormone use were all positively associated with malignant carcinoid tumors of the small intestine. Furthermore, we observed elevated, but not statistically significant, risks for carcinoid tumors among those with a family history of any cancer or colorectal cancer, and among those with a personal history of colorectal polyps. Identifying risk factors for small intestinal cancer from a prospective study is important because so little is known about this cancer, which is increasing in the U.S. [2] and in Northern Europe [14]. Our study also highlights the importance of studying this cancer by the two main histologic subtypes. In the 1970s carcinoids tumors represented 27% of all small intestinal tumors in the U.S., by 1998-2002 this had increased to 39% [10]. Using *Surveillance Epidemiology and End Results* (SEER) U.S. data, the overall incidence of carcinoid tumors of the small intestine increased 4-fold between 1973 and 2004, yet the five-year survival rates have remained the same [10].

Previous epidemiologic studies of small intestinal cancer have been case-control studies, except one pooled prospective study in Asia [15], and most have not investigated this malignancy by the two main histologic subtypes: adenocarcinomas and carcinoid tumors, which may have different etiologies. With the exception of two dietary studies in our cohort [16, 17], the only previous epidemiologic study that examined small intestinal cancer by both histologic subtypes was a hospital-based case-control study with just 19 adenocarcinomas and 17 malignant carcinoid tumors [18]. Other epidemiologic studies have reported on adenocarcinomas only [19-21] and were all small studies with 23, 36 and 70 cases, respectively; carcinoids only [22]; and one study investigated risk factors for dying of small intestinal cancer [23]. Our data is not only from a large prospective study with greater statistical power to detect associations than previous studies, but it also provides data by histologic subtype.

The age standardized incidence rates for small intestinal cancer were marginally lower in our cohort compared to the rates reported in SEER (7.2 and 5.4 per 100,000 men and women, respectively, per year) for individual's ≥ 50 years old in 2006, which was the last year of follow-up in our study [3]. The slightly lower incidence in our cohort could be explained by differences in population characteristics; people who voluntarily participated in our study, as well as other cohort studies, tend to have a healthier lifestyle and a higher socioeconomic status than those of the general population (e.g. SEER population).

A study using SEER data revealed that both adenocarcinomas and carcinoid tumors of the small intestine were more common in men than women [incidence rate ratio and 95% CI: 1.45 (1.35, 1.55); 1.42 (1.34, 1.51), respectively], and in Blacks compared to Whites [incidence rate ratio and 95% CI: 2.06 (1.87, 2.26); 1.63 (1.50, 1.78), respectively] [24]; our study confirmed these descriptive data for sex for carcinoid tumors, but not for adenocarcinomas or race. It is not clear why our data was not concordant with the data from SEER for adenocarcinomas in men; one possible explanation is the limited number of adenocarcinoma cases in our study (n=25 cases in women and n=59 cases in men). Furthermore, even though our cohort was large, we only ascertained 5 adenocarcinoma cases among Blacks and 4 malignant carcinoid cases among Blacks; therefore, it is difficult to draw conclusions regarding race from our analysis. In contrast to our study and the data from SEER, one case-control study of carcinoid tumors found an increased risk in women and those 60 years or younger [22]. Our observation that the incidence of small intestinal carcinoid tumors was higher in men compared to women, couple with our finding that menopausal hormone therapy was positively associated with these tumors suggests that sex hormones may play a role in the development of this malignancy. We note, however, that no other data exist to support this finding and that it contrasts with a substantial body of literature supporting an inverse relationship between menopausal hormone therapy and colorectal cancer [25-27]. The findings from our study suggest that sex differences and hormones should be further investigated by examining these variables in other prospective studies, and investigating the effect of type and duration of hormone use, as potential etiologic factors for carcinoid tumors of the small intestine.

The international incidence of small intestinal cancer and colorectal cancer are correlated, suggesting that these malignancies may share common risk factors [7]. Prior case-control studies of BMI in relation to adenocarcinomas and carcinoid tumors of the small intestine have found contrasting findings to our study; while we observed a positive association between BMI and carcinoid tumors, which is in agreement with data for colorectal cancer [28], others have reported inverse associations for adenocarcinomas and carcinoid tumors of the small intestine [20, 22]. A possible explanation for these conflicting results may lie in the study design; unlike our study, the previous investigations were case-control studies that assessed BMI at the time the cancer was diagnosed and, therefore, it is possible that the results were biased by reverse causality. The only other prospective study of small intestinal cancer was a pooled analysis of cohort studies within Asia, and although they did not present results by histologic subtype due to a limited number of cases (49 adenocarcinomas and 11 carcinoids), they did observe elevated risk estimates for small intestinal cancer among those with a higher BMI, but the data was not statistical significant [15]. Although our findings require replication, they do add support to the increasing number of chronic diseases related to obesity.

Only one previous study reported on education in relation to small intestinal cancer and, similar to our findings for both histologic subtypes, they found no association for adenocarcinomas [20]. While the positive associations we observed between family history of cancer (any cancer, and colorectal cancer specifically) and malignant carcinoid tumors of the small intestine did not reach statistical significance, a previous case-control study reported a statistically significant associations where the odds ratio for a family history of any cancer was 1.7 (95% CI: 1.2, 2.4) and for a family history of colorectal cancer was 1.7 (95% CI: 1.0, 2.9) [29]. Taken together, these findings indicate that family history of cancer could be an important factor in small intestinal cancer, and warrants further study.

Of the limited number of epidemiologic investigations of lifestyle factors and small intestinal cancer, smoking was positively associated with both adenocarcinomas and carcinoid tumors in one small study [18, 21], but not in others [19-23], including ours. In

agreement with our study, case-control studies of adenocarcinomas [19, 20] and carcinoid tumors [22] found no association for alcohol intake, although two studies did report a positive association for both adenocarcinomas [18, 21] and carcinoid tumors [18]. Furthermore, neither smoking nor alcohol intake were associated with dying from small intestinal cancer in men or women [23]. The main difference between our study and previous studies is a larger number of cases, and the prospective design of our study, which enabled the collection of demographic and lifestyle factors prior to the onset of disease; previous studies have collected exposure data after the onset of disease, which can result in reporting bias and reverse causation.

Adenocarcinomas of the small intestine likely arise from the adenoma-carcinoma sequence [30], from which the overwhelming majority of colorectal cancers arise; therefore, it is somewhat surprising that none of the known risk factors for adenocarcinoma of the colorectum appear to be associated with adenocarcinoma of the small intestine in our study. Smoking, BMI, and alcohol have all been positively associated with colorectal adenocarcinoma, and diabetes, physical activity, and menopausal hormone therapy have been inversely associated [31]; however, with regard to small intestinal adenocarcinoma, all of these associations in our study were null. Whilst our study is the largest prospective study of this malignancy conducted to date, we may have had an insufficient number of adenocarcinoma cases to detect associations; for example, there were only 10 current smokers who developed adenocarcinomas and only 6 adenocarcinoma cases with a BMI of 35 kg/m^2 or greater at baseline. Future studies should consider pooling data from large prospective studies to improve statistical power for analyses by histologic subtype.

The principal strengths of our study include the size of the cohort, which enabled us to conduct one of the first prospective studies of demographic and lifestyle factors and small intestinal cancer. Recall bias and reverse causation were minimized in this study by the prospective design and exposure assessment prior to cancer diagnosis. Potential limitations include the small number of cases by histologic subtype in some exposure categories, which could result in instability in our risk estimates, as well as some measurement error associated with self-reported assessment of lifestyle variables, which could result in attenuated risk estimates. Furthermore, we lacked information on specific conditions that are known risk factors for adenocarcinoma of the small intestine, such as familial adenomatous polyposis, celiac disease, and Crohns disease, which restricted our ability to investigate some of these more established risk factors and may also have resulted in attenuated risk estimates [18, 32].

To conclude, we report data to demonstrate that adenocarcinomas and carcinoid tumors of the small intestine have different etiologies. The only risk factor we identified for adenocarcinoma was age at baseline; whereas age at baseline, male sex, BMI, and menopausal hormone therapy use were all positively associated with carcinoid tumors of the small intestine, in addition to some other suggestive associations regarding family history of cancer, and history of colorectal polyps. Identifying modifiable risk factors for carcinoid tumors could decrease the risk of other malignancies, since individuals with a carcinoid tumor of the small intestine have a three-fold higher risk of developing colorectal cancer and a 60% increased risk of developing any other malignancy [4, 33]. The associations identified in this study should be considered exploratory and need to be further investigated in a study with a larger number of cases by pooling existing studies with relevant data.

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Abbreviations

CI	confidence interval
BMI	body mass index
HR	hazards ratio

REFERENCES

1. Parkin, DM.; Whelan, SL.; Ferlay, J.; Teppo, DB. Cancer Incidence in Five Continents. Vol. VIII. IARC Scientific Publications; Lyon, France: 2002.
2. Ries, LAG.; Harkins, D.; Krapcho, M.; Mariotto, A.; Miller, BA.; Feuer, EJ.; Clegg, L.; Eisner, MP.; Horner, MJ.; Howlader, N.; Hayat, M.; Hankey, BF.; Edwards, BK. SEER Cancer Statistics Review, 1975-2003. National Cancer Institute; Bethesda, MD: 2006. http://seer.cancer.gov/csr/1975_2003/
3. Howlader NNA, Krapcho M, Garshell J, Neyman N, Altekruse SF, Kosary CL, Yu M, Ruhl J, Tatalovich Z, Cho H, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA. SEER Cancer Statistics Review, 1975-2010. National Cancer InstituteBethesda, MDhttp://seer.cancer.gov/csr/1975_2010/, based on November 2012 SEER data submission, posted to the SEER web site, 2013.
4. Scelo G, Boffetta P, Hemminki K, Pukkala E, Olsen JH, Andersen A, Tracey E, Brewster DH, McBride ML, Kliewer EV, Tonita JM, Pompe-Kirn V, Chia KS, Jonasson JG, Martos C, Colin D, Brennan P. Associations between small intestine cancer and other primary cancers: an international population-based study. Int J Cancer. 2006; 118:189–96. [PubMed: 16003748]
5. Schottenfeld, D.; Fraumeni, JF. Cancer Epidemiology and Prevention. Oxford University Press; New York: 2006.
6. Bilimoria KY, Bentrem DJ, Wayne JD, Ko CY, Bennett CL, Talamonti MS. Small bowel cancer in the United States: changes in epidemiology, treatment, and survival over the last 20 years. Ann Surg. 2009; 249:63–71. [PubMed: 19106677]
7. Haselkorn T, Whittemore AS, Lilienfeld DE. Incidence of small bowel cancer in the United States and worldwide: geographic, temporal, and racial differences. Cancer Causes Control. 2005; 16:781–7. [PubMed: 16132788]
8. Schottenfeld D, Beebe-Dimmer JL, Vigneau FD. The epidemiology and pathogenesis of neoplasia in the small intestine. Ann Epidemiol. 2009; 19:58–69. [PubMed: 19064190]

9. Ries, LA.; Young, JL.; Keel, GE.; Eisner, MP.; Lin, YD.; Horner, MJ. SEER survival monograph: Cancer survival among adults: U.S. SEER Program, 1988-2001, patient and tumor characteristics. National Cancer Institute; Bethesda, MD: 2007.
10. Modlin IM, Champaneria MC, Chan AK, Kidd M. A three-decade analysis of 3,911 small intestinal neuroendocrine tumors: the rapid pace of no progress. Am J Gastroenterol. 2007; 102:1464–73. [PubMed: 17391319]
11. Schatzkin A, Subar AF, Thompson FE, Harlan LC, Tangrea J, Hollenbeck AR, Hurwitz PE, Coyle L, Schussler N, Michaud DS, Freedman LS, Brown CC, Midthune D, Kipnis V. Design and serendipity in establishing a large cohort with wide dietary intake distributions : the National Institutes of Health-American Association of Retired Persons Diet and Health Study. Am J Epidemiol. 2001; 154:1119–25. [PubMed: 11744517]
12. Michaud DS, Midthune D, Hermansen S, Leitzmann MF, Harlan LC, Kipnis V. Comparison of cancer registry case ascertainment with SEER estimates and self-reporting in a subset of the NIH-AARP Diet and Health Study. Journal of Registry Management. 2005; 32:70–7. al. E.
13. International Classification of Diseases for Oncology. Third edition. World Health Organization; Geneva: 2000.
14. Shack LG, Wood HE, Kang JY, Brewster DH, Quinn MJ, Maxwell JD, Majeed A. Small intestinal cancer in England & Wales and Scotland: time trends in incidence, mortality and survival. Aliment Pharmacol Ther. 2006; 23:1297–306. [PubMed: 16629934]
15. Boffetta P, Hazelton WD, Chen Y, Sinha R, Inoue M, Gao YT, Koh WP, Shu XO, Grant EJ, Tsuji I, Nishino Y, You SL, Yoo KY, Yuan JM, Kim J, Tsugane S, Yang G, Wang R, Xiang YB, Ozasa K, Nagai M, Kakizaki M, Chen CJ, Park SK, Shin A, Ahsan H, Qu CX, Lee JE, Thornquist M, Rolland B, Feng Z, Zheng W, Potter JD. Body mass, tobacco smoking, alcohol drinking and risk of cancer of the small intestine--a pooled analysis of over 500,000 subjects in the Asia Cohort Consortium. Ann Oncol. 2012; 23:1894–8. [PubMed: 22147734]
16. Cross AJ, Leitzmann MF, Subar AF, Thompson FE, Hollenbeck AR, Schatzkin A. A prospective study of meat and fat intake in relation to small intestinal cancer. Cancer Res. 2008; 68:9274–9. [PubMed: 19010900]
17. Schatzkin A, Park Y, Leitzmann MF, Hollenbeck AR, Cross AJ. Prospective study of dietary fiber, whole grain foods, and small intestinal cancer. Gastroenterology. 2008; 135:1163–7. [PubMed: 18727930]
18. Chen CC, Neugut AI, Rotterdam H. Risk factors for adenocarcinomas and malignant carcinoids of the small intestine: preliminary findings. Cancer Epidemiol Biomarkers Prev. 1994; 3:205–7. [PubMed: 8019367]
19. Kaerlev L, Teglbjaerg PS, Sabroe S, Kolstad HA, Ahrens W, Eriksson M, Guenel P, Hardell L, Launoy G, Merler E, Merletti F, Stang A, Olsen J. Is there an association between alcohol intake or smoking and small bowel adenocarcinoma? Results from a European multi-center case-control study. Cancer Causes Control. 2000; 11:791–7. [PubMed: 11075867]
20. Negri E, Bosetti C, La Vecchia C, Fioretti F, Conti E, Franceschi S. Risk factors for adenocarcinoma of the small intestine. Int J Cancer. 1999; 82:171–4. [PubMed: 10389747]
21. Wu AH, Yu MC, Mack TM. Smoking, alcohol use, dietary factors and risk of small intestinal adenocarcinoma. Int J Cancer. 1997; 70:512–7. [PubMed: 9052748]
22. Hassan MM, Phan A, Li D, Dagohoy CG, Leary C, Yao JC. Risk factors associated with neuroendocrine tumors: A U.S.-based case-control study. Int J Cancer. 2008; 123:867–73. [PubMed: 18491401]
23. Chow WH, Linet MS, McLaughlin JK, Hsing AW, Chien HT, Blot WJ. Risk factors for small intestine cancer. Cancer Causes Control. 1993; 4:163–9. [PubMed: 8481495]
24. Qubaiah O, Devesa SS, Platz CE, Huycke MM, Dores GM. Small intestinal cancer: a population-based study of incidence and survival patterns in the United States, 1992 to 2006. Cancer Epidemiol Biomarkers Prev. 2010; 19:1908–18. [PubMed: 20647399]
25. Chlebowski RT, Wactawski-Wende J, Ritenbaugh C, Hubbell FA, Ascensao J, Rodabough RJ, Rosenberg CA, Taylor VM, Harris R, Chen C, Adams-Campbell LL, White E. Estrogen plus progestin and colorectal cancer in postmenopausal women. N Engl J Med. 2004; 350:991–1004. [PubMed: 14999111]

26. Green J, Czanner G, Reeves G, Watson J, Wise L, Roddam A, Beral V. Menopausal hormone therapy and risk of gastrointestinal cancer: Nested case-control study within a prospective cohort, and meta-analysis. Int J Cancer. 2011
27. Grodstein F, Newcomb PA, Stampfer MJ. Postmenopausal hormone therapy and the risk of colorectal cancer: a review and meta-analysis. Am J Med. 1999; 106:574–82. [PubMed: 10335731]
28. WCRF/AICR. World Cancer Research Fund / American Institute for Cancer Research. Continuous Update Project. Food, Nutrition, Physical Activity, and the Prevention of Colorectal Cancer. Washington, D.C.: 2011.
29. Hassan MM, Phan A, Li D, Dagohoy CG, Leary C, Yao JC. Family history of cancer and associated risk of developing neuroendocrine tumors: a case-control study. Cancer Epidemiol Biomarkers Prev. 2008; 17:959–65. [PubMed: 18398037]
30. Sellner F. Investigations on the significance of the adenoma-carcinoma sequence in the small bowel. Cancer. 1990; 66:702–15. [PubMed: 2167140]
31. Kahi CJ, Rex DK, Imperiale TF. Screening, surveillance, and primary prevention for colorectal cancer: a review of the recent literature. Gastroenterology. 2008; 135:380–99. [PubMed: 18582467]
32. Neugut AI, Jacobson JS, Suh S, Mukherjee R, Arber N. The epidemiology of cancer of the small bowel. Cancer Epidemiol Biomarkers Prev. 1998; 7:243–51. [PubMed: 9521441]
33. Babovic-Vuksanovic D, Constantinou CL, Rubin J, Rowland CM, Schaid DJ, Karnes PS. Familial occurrence of carcinoid tumors and association with other malignant neoplasms. Cancer Epidemiol Biomarkers Prev. 1999; 8:715–9. [PubMed: 10744132]

Table 1

Characteristics of the Cohort and the Cases (means unless otherwise stated as proportions)

	Cohort	Adenocarcinomas	Carcinoids
Men	***n=297,250***	***n=59***	***n=70***
Age at baseline (years)	62.1	64.7	63.7
Race			
Non-Hispanic white (%)	92.4	91.5	95.7
Non-Hispanic black (%)	2.8	3.4	2.9
Hispanic (%)	1.9	1.7	0
Asian (%)	1.3	0	0
Pacific Islander, American Indian, Alaskan native or unknown (%)	1.6	3.4	0
Education, college graduate or post graduate (%)	44.3	45.8	54.3
Positive family history of any cancer (%)	46.9	47.5	57.1
Positive family history of colorectal cancer (%)	8.2	11.9	14.3
Personal history of colorectal polyps (%)	11.0	13.6	15.7
Diabetes (%)	10.1	13.6	10.0
Currently married (%)	84.8	88.1	85.7
Smoking history			
Never smoker (%)	29.0	25.4	22.9
Former smoker (%)	54.7	59.3	67.1
Current smoker or having quit < 1 year ago (%)	12.2	10.2	5.7
Body mass index (kg/m^2)	27.3	26.8	28.0
Vigorous physical activity, ≥5 times per week (%)	21.3	17.0	22.9
Alcohol intake (g/day)	18.0	19.6	16.7
Multivitamin use (%)	51.6	61.0	60.0
Women	***n=201,126***	***n=25***	***n=54***
Age at baseline (years)	61.8	61.9	63.2
Race			
Non-Hispanic white (%)	89.1	84.0	94.4
Non-Hispanic black (%)	5.8	12.0	3.7
Hispanic (%)	1.9	4.0	1.9
Asian (%)	1.1	0	0
Pacific Islander, American Indian, Alaskan native or unknown (%)	2.1	0	0
Education, college graduate or post graduate (%)	29.6	20.0	25.9
Positive family history of any cancer (%)	51.0	36.0	59.3
Positive family history of colorectal cancer (%)	9.4	4.0	14.8
Personal history of colorectal polyps (%)	6.5	4.0	14.8
Diabetes (%)	7.4	4.0	11.1
Currently married (%)	44.2	56.0	44.4
Smoking history			
Never smoker (%)	43.9	32.0	51.9
Former smoker (%)	36.2	52.0	31.5

	Cohort	Adenocarcinomas	Carcinoids
Current smoker or having quit < 1 year ago (%)	16.2	16.0	11.1
Body mass index (kg/m^2)	26.9	28.6	27.9
Vigorous physical activity, ≥5 times per week (%)	16.2	12.0	18.5
Alcohol intake (g/day)	6.0	7.3	7.6
Multivitamin use (%)	60.2	52.0	50.0
Menopausal hormone therapy use			
Former (%)	8.9	4.0	14.8
Current (%)	44.0	28.0	50.0

Table 2

Hazard Ratio[a] (95% Confidence Intervals) for Small Intestinal Cancer by Demographic Characteristics

	Total (n=237)		Adenocarcinomas (n=84)		Carcinoids (n=124)	
	Cases	**HR (95% CI)**	**Cases**	**HR (95% CI)**	**Cases**	**HR (95% CI)**
Females	90	Ref	25	Ref	54	Ref
Males	147	1.13 (0.87, 1.48)	59	0.78 (0.49, 1.25)	70	1.44 (1.01, 2.05)
Age at baseline (years, categorical)						
50-<55	14	Ref	6	Ref	7	Ref
55-59	44	1.93 (1.06, 3.53)	14	1.43 (0.55, 3.72)	25	2.20 (0.95, 5.09)
60-64	68	2.51 (1.41, 4.45)	20	1.71 (0.69, 4.27)	38	2.81 (1.25, 6.29)
≥65	111	3.39 (1.94, 5.91)	44	3.12 (1.33, 7.31)	54	3.31 (1.51, 7.28)
Age at baseline (years, continuous)	237	1.07 (1.04, 1.10)	84	1.08 (1.03, 1.13)	124	1.06 (1.03, 1.10)
P-trend		<0.0001		0.0007		0.0006
Race						
Non-Hispanic White	221	Ref	75	Ref	118	Ref
Non-Hispanic Black	9	1.09 (0.56, 2.13)	5	1.94 (0.78, 4.82)	4	0.86 (0.32, 2.34)
Hispanic	3	0.79 (0.25, 2.46)	2	1.54 (0.38, 6.28)	1	0.49 (0.07, 3.53)
Asian	1	0.40 (0.06, 2.85)	0	-	1	0.76 (0.11, 5.43)
Other	3	0.64 (0.21, 2.00)	2	-	0	-
Global P-value[b]		0.723		0.146		0.124
Education[c]						
Less than high school	70	Ref	30	Ref	30	Ref
Post high school	19	0.77 (0.46, 1.27)	5	0.46 (0.18, 1.19)	13	1.25 (0.65, 2.39)
Some college	46	0.82 (0.57, 1.20)	14	0.57 (0.30, 1.08)	26	1.11 (0.65, 1.87)
College / postgraduate	93	1.04 (0.76, 1.42)	32	0.77 (0.47, 1.28)	52	1.42 (0.90, 2.25)
P-trend		0.754		0.377		0.268
Family history of cancer						
No	113	Ref	47	Ref	52	Ref
Yes	124	1.14 (0.88, 1.47)	37	0.83 (0.54, 1.28)	72	1.42 (0.99, 2.03)
Family history of colorectal cancer[c]						
No	200	Ref	73	Ref	105	Ref
Yes	29	1.37 (0.93, 2.02)	8	1.05 (0.51, 2.19)	18	1.61 (0.97, 2.65)
Personal history of colorectal polyps						
No	204	Ref	75	Ref	105	Ref
Yes	33	1.30 (0.90, 1.88)	9	0.92 (0.46, 1.84)	19	1.51 (0.92, 2.46)
Diabetes						
No	215	Ref	75	Ref	111	Ref
Yes	22	0.76 (0.49, 1.18)	9	0.88 (0.44, 1.76)	13	0.88 (0.50, 1.57)

[a] Hazard ratios adjusted for age, gender, and follow-up time (except the model giving risk estimates for gender, which was adjusted for age and follow-up time)

[b] Global P-value calculated using Chi^2 test with the appropriate degrees of freedom for each model

[c] Cases do not add to total due to missing data

Table 3

Hazard Ratio[a] (95% Confidence Intervals) for Small Intestinal Cancer by Modifiable Characteristics

	Total (n=237)		Adenocarcinomas (n=84)		Carcinoids (n=124)	
	Cases	**HR (95% CI)**	**Cases**	**HR (95% CI)**	**Cases**	**HR (95% CI)**
Smoking[c]						
Never smoker	73	Ref	23	Ref	44	Ref
Quit ≥ 10 years ago	99	1.11 (0.81, 1.51)	36	1.18 (0.69, 2.01)	55	1.09 (0.72, 1.63)
Quit 1 to 9 years ago	30	1.08 (0.71, 1.66)	12	1.33 (0.66, 2.68)	9	0.54 (0.27, 1.12)
Current smoker, ≤20 cigs/day	15	0.66 (0.38, 1.16)	7	1.00 (0.43, 2.33)	6	0.43 (0.19, 1.02)
Current smoker, >20 cigs/day	9	0.72 (0.36, 1.45)	3	0.74 (0.22, 2.47)	4	0.54 (0.19, 1.51)
P-trend		0.355		0.779		0.071
BMI (kg/m^2)[c]						
18.5 to <25	76	Ref	27	Ref	41	Ref
25 to <30	99	1.06 (0.78, 1.44)	39	1.12 (0.68, 1.84)	45	0.92 (0.60, 1.42)
30 to <35	32	0.96 (0.63, 1.45)	9	0.74 (0.35, 1.57)	20	1.13 (0.66, 1.92)
≥35	23	1.77 (1.11, 2.82)	6	1.35 (0.56, 3.28)	14	1.95 (1.06, 3.58)
P-trend[b]		0.028		0.617		0.025
Vigorous physical activity (hours)						
Never/rarely	61	Ref	21	Ref	33	Ref
1-3 /month	38	1.13 (0.75, 1.69)	12	1.00 (0.49, 2.03)	21	1.17 (0.68, 2.03)
1-2/week	37	0.67 (0.45, 1.01)	16	0.81 (0.42, 1.55)	18	0.62 (0.35, 1.11)
3-4/week	56	0.77 (0.54, 1.11)	22	0.83 (0.46, 1.52)	26	0.69 (0.41, 1.15)
≥5/week	45	0.85 (0.58, 1.26)	13	0.67 (0.33, 1.34)	26	0.95 (0.57, 1.60)
P-trend		0.130		0.232		0.305
Alcohol (g/day)						
0	14	Ref	5	Ref	7	Ref
>0 to <5	136	1.56 (0.90, 2.71)	44	1.39 (0.55, 3.51)	75	1.74 (0.80, 3.78)
5 to <15	34	1.46 (0.78, 2.73)	12	1.36 (0.48, 3.87)	19	1.70 (0.71, 4.06)
15 to <30	26	1.49 (0.77, 2.86)	11	1.62 (0.56, 4.68)	9	1.09 (0.41, 2.95)
≥30	27	1.53 (0.80, 2.93)	12	1.71 (0.60, 4.90)	14	1.70 (0.68, 4.26)
P-trend		0.640		0.340		0.987
Multivitamin use[c]						
No	34	Ref	11	Ref	20	Ref
Yes	135	1.19 (0.82, 1.73)	49	1.34 (0.70, 2.57)	69	1.03 (0.63, 1.70)
Menopausal hormone therapy use[d]						
Never	42	Ref	17	Ref	19	Ref
Former	9	1.17 (0.57, 2.40)	1	0.32 (0.04, 2.40)	8	2.29 (1.00, 5.24)
Current	39	1.24 (0.80, 1.93)	7	0.51 (0.21, 1.24)	27	1.94 (1.07, 3.50)
P-trend		0.333		0.117		0.028

[a]Hazard ratios adjusted for age, gender, and follow-up time (except the model giving risk estimates for gender, which was adjusted for age and follow-up time)

[b] Based on continuous data

[c] Cases do not add to total due to missing data

[d] Among women