Annals of Oncology

Annals of Oncology 23: 1894–1898, 2012
doi:10.1093/annonc/mdr562
Published online 6 December 2011

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

P. Boffetta[1,2*], W. D. Hazelton[3], Y. Chen[4], R. Sinha[5], M. Inoue[6], Y. T. Gao[7], W. P. Koh[8], X. O. Shu[9], E. J. Grant[10], I. Tsuji[11], Y. Nishino[12], S. L. You[13], K. Y. Yoo[14], J. M. Yuan[15], J. Kim[16], S. Tsugane[6], G. Yang[9], R. Wang[15], Y. B. Xiang[7], K Ozasa[10], M. Nagai[11], M. Kakizaki[11], C. J. Chen[17], S. K. Park[18], A. Shin[16], H. Ahsan[19,20,21,22], C. X. Qu[23], J. E. Lee[24], M. Thornquist[3], B. Rolland[3], Z. Feng[3], W. Zheng[9] & J. D. Potter[3,25]

[1]The Tisch Cancer Institute and Institute for Translational Epidemiology, Mount Sinai School of Medicine, New York, USA; [2]International Prevention Research Institute, Lyon, France; [3]Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle; [4]Department of Environmental Medicine, New York University School of Medicine, New York; [5]Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, USA; [6]Epidemiology and Prevention Division, Research Center for Cancer Prevention and Screening, National Cancer Center, Tokyo, Japan; [7]Department of Epidemiology, Shanghai Cancer Institute, Shanghai, China; [8]Department of Epidemiology and Public Health, Yong Loo Lin School of Medicine, National University of Singapore, Singapore; [9]Division of Epidemiology, Department of Medicine, Vanderbilt Epidemiology Center, Vanderbilt-Ingram Cancer Center, Vanderbilt University School of Medicine, Nashville, USA; [10]Department of Epidemiology, Radiation Effects Research Foundation, Hiroshima; [11]Division of Epidemiology, Department of Public Health and Forensic Medicine, Tohoku University Graduate School of Medicine, Miyagi; [12]Department of Epidemiology, Miyagi Cancer Center Research Institute, Miyagi, Japan; [13]Genomics Research Center, Academia Sinica and School of Public Health, National Defense Medical Center, Taipei, Taiwan; [14]Department of Preventive Medicine, Seoul National University College of Medicine, Seoul, Korea; [15]Masonic Cancer Center, University of Minnesota, Minneapolis, USA; [16]Cancer Epidemiology Branch, National Cancer Center, Seoul, Korea; [17]Genomics Research Center, Academia Sinica and Graduate Institute of Epidemiology, College of Public Health, National Taiwan University, Taipei, Taiwan; [18]Department of Preventive Medicine, Seoul National University College of Medicine, Cancer Research Institute, Seoul National University and Department of Biomedical Science, Seoul National University Graduate School, Korea; [19]Departments of Health Studies; [20]Medicine and; [21]Human Genetics and; [22]Cancer Research Center, The University of Chicago, Chicago, USA; [23]Chinese Academy of Medical Sciences and Peking Union Medical College, Department of Cancer Epidemiology, Cancer Institute/Hospital, Beijing, China; [24]Sookmyung Women's University, Seoul, Korea; [25]Centre for Public Health Research, Massey University, Wellington, New Zealand

Received 12 August 2011; revised 15 October 2011; accepted 17 October 2011

Background: The evidence for a role of tobacco smoking, alcohol drinking, and body mass index (BMI) in the etiology of small intestine cancer is based mainly on case–control studies from Europe and United States.
Subjects and methods: We harmonized the data across 12 cohort studies from mainland China, Japan, Korea, Singapore, and Taiwan, comprising over 500 000 subjects followed for an average of 10.6 years. We calculated hazard ratios (HRs) for BMI and (only among men) tobacco smoking and alcohol drinking.
Results: A total of 134 incident cases were observed (49 adenocarcinoma, 11 carcinoid, 46 other histologic types, and 28 of unknown histology). There was a statistically non-significant trend toward increased HR in subjects with high BMI [HR for BMI >27.5 kg/m^2, compared with 22.6–25.0, 1.50; 95% confidence interval (CI) 0.76–2.96]. No association was suggested for tobacco smoking; men drinking >400 g of ethanol per week had an HR of 1.57 (95% CI 0.66–3.70), compared with abstainers.
Conclusions: Our study supports the hypothesis that elevated BMI may be a risk factor for small intestine cancer. An etiologic role of alcohol drinking was suggested. Our results reinforce the existing evidence that the epidemiology of small intestine cancer resembles that of colorectal cancer.
Key words: alcohol drinking, body mass index, prospective studies, small intestine cancer, tobacco smoking

introduction

The burden of cancer has greatly increased in Asia in recent decades, and the pattern has become closer to that observed in Europe and North America as a consequence of: (i) increase in population size; (ii) aging of the population; and (iii) changes in the pattern of risk factors, including tobacco, alcohol, obesity, reproductive habits, and occupational agents [1]. Epidemiologic studies conducted in populations in Asia have stressed the role of changes in risk factors in determining the rapid change in cancer risk, particularly in urban populations.

*Correspondence to: Dr P. Boffetta, The Tisch Cancer Institute, Mount Sinai School of Medicine, One Gustave L. Levy Place, Box 1079, New York, NY 10029, USA. Tel: +1-212-824-7073; Fax: +1-212-876-6789; E-mail: paolo.boffetta@mssm.edu

© The Author 2011. Published by Oxford University Press on behalf of the European Society for Medical Oncology.
All rights reserved. For permissions, please email: journals.permissions@oup.com.

Downloaded from http://annonc.oxfordjournals.org/ at Fred Hutchinson Cancer Research Ctr on August 23, 2013

It is important to evaluate the impact of these risk factors on specific cancers using well-designed prospective studies. Some of the cancers, however, are too rare to be efficiently studied in a single investigation.

We established the Asia Cohort Consortium to foster cancer epidemiology research in populations in transition among Asian countries through multicenter pooling of data from different cohort studies. Such a collaborative approach is particularly useful for the study of relatively rare neoplasms, for which data from individual cohorts have limited statistical power. Among rare neoplasms of interest is cancer of the small intestine. In 1998–2002, the age-standardized incidence of cancer of the small intestine in Asian countries was in the range of 0.3–1.3/100 000 [2], with evidence of an increase in the last decades [3]. The two main histologic types of small intestine cancer are adenocarcinoma and carcinoid, each comprising about one-third of total cases in European and American populations; lymphomas and sarcomas comprise the majority of the remaining cases [4]. Only limited data are available on the histologic distribution of small intestine cancer, particularly in Asian populations.

Current knowledge on the causes of small intestine cancer, as is the case for other rare cancers, is hampered by the difficulty of assembling a series of cases that is large enough. All available studies have been conducted in Europe and North America. Crohn's disease (CD) is associated with adenocarcinoma of the small intestine: CD patients have a 27-fold increased risk of small intestine adenocarcinoma [5]. However, the prevalence of CD is relatively low in Asian countries (in the range of 3–21/100 000 [6–8]), resulting in an attributable fraction of <1% of small intestine cancers. The roles of the other medical conditions associated with small intestine adenocarcinoma, including Peutz–Jeghers syndrome, familial adenomatous polyposis, and acromegaly, are even less important at the population level. Environmental factors suggested to be causally associated with cancer of the small intestine include tobacco smoking, alcohol drinking, elevated body mass index (BMI) [9–17], and dietary factors, including low intake of grain and wholegrain foods [18] and high intake of meat [10, 12, 19] and saturated fat [19]. Available studies, however, are almost exclusively of case–control design, often of small size, and their results are not fully consistent.

The association between BMI and cancer of the small intestine has been investigated in a large cohort study including >1000 cases [17]; in contrast, tobacco smoking and alcohol drinking have been investigated only in two smaller prospective studies, including 49 and 17 cases [14, 16]. All available studies to date were from Europe and North America. The aim of this study was to investigate the role of tobacco smoking, alcohol drinking, and high BMI in the etiology of cancer of the small intestine in a pooled analysis of prospective cohort studies from Asian populations.

methods

The study was based on the pooling of data from 12 cohort studies from mainland China, Japan, Korea, Singapore, and Taiwan. Selected characteristics of the cohorts are summarized in Appendix Table A1 (available as supplementary data at *Annals of Oncology* online). The size of the cohorts varied from 15 000 to 75 000 subjects, the period of enrollment was mainly during the 1990s and early 2000s, and the end of the follow-up was 2006 or later in all but two cohorts.

Questionnaires and study protocols were collected from participating studies to assess the variables to be pooled, including the main risk factors of interest (cigarette smoking, alcohol drinking, BMI), as well as potential confounders (sex, age, education). The outcome of interest was incidence of cancer of the small intestine (ICD-10, C17); information on histology was collected if available. Subjects were considered at risk from enrollment in the cohort until death, censoring (e.g. loss to follow-up, emigration), or end of follow-up, whichever occurred earliest.

Subjects were categorized as never versus ever smokers: the latter group was divided into current and former smokers, as well as according to cumulative tobacco smoking, expressed as pack-years (0.1–20.0, 20.1–29.9, and 30.0 + pack-years). A similar classification was used for alcohol use (never and ever drinkers, the latter group classified according to average weekly intake of ethanol: 0.1–100.0, 100.1–400.0, and 400.1 + g/week, after transformation of intake of different alcoholic beverages into grams of ethanol). BMI was calculated as weight [kg]/(height [m])^2 and categorized as follows: <20.0, 20.1–22.5, 22.6–25.0, 25.1–27.5, and 27.6 + kg/m^2. The category 22.6–25.0 was chosen as reference, based on the results of a pooled an analysis of BMI and overall mortality that included most of these cohorts [20]. We also conducted a sensitivity analysis based on sex-specific quartiles of the BMI distribution rather than on pre-defined categories.

In order to investigate the combined effect of the three risk factors included in our analysis, we calculated a 'combined risk score' by assigning a 0/1 score to each of the three risk factors under investigation; a score of 1 was assigned to subjects in the a priori high-risk categories for each risk factor: BMI >25.0 kg/m^2; ever smoking; and drinking >400 g of alcohol per week. The combined risk score therefore ranged from 0 (reference category) to 3. This analysis was restricted to men because of the low prevalence of tobacco smoking and alcohol drinking among women in these Asian cohorts.

The main associations with potential risk factors were measured by estimating hazard ratios (HRs) and 95% confidence intervals (CIs) based on Poisson regression with random effects in log-linear hazard models [21]. The primary outcome was incidence of small intestine cancer. Secondary analysis included investigating small intestine adenocarcinoma cases, consisting of ICD-O histology codes 814-821 and 826. We assumed that the cases occurred through a Poisson process, assuming an exponential survival distribution and categorical variables for BMI, tobacco smoking, alcohol drinking, and age. We used the GLIMMIX procedure in SAS 9.2 for generalized linear mixed models, assuming Gaussian random effects to account for heterogeneity among cohorts, to estimate model parameters, and for statistical inference. For a given risk factor of interest (e.g. tobacco smoking), potential confounders included age, sex, and highest level of education attainment, as well as the other risk factors under study (in this instance, BMI and alcohol drinking). No imputation was done for missing data. Likelihood-based methods were used to test for heterogeneity across studies or geographic regions by comparing models with and without interactions between cohort or geographic region and potential risk factors (BMI, alcohol, and smoking). Stratified analyses were performed by region: mainland China, Singapore, and Taiwan together; Japan.

results

The main characteristics of the overall study population are reported in Table 1 and cohort-specific information in Appendix Table A1 (available as supplementary data at *Annals of Oncology* online). Overall, the pooled analyses included 527 726 subjects, who contributed 5606 048 person-years of

Downloaded from http://annonc.oxfordjournals.org/ at Fred Hutchinson Cancer Research Ctr on August 23, 2013

Table 1. Descriptive characteristics of the study population

	N of subjects	*N* of person-years	*N* of cases
Sex			
Male	251 753	2 451 365	87
Female	275 973	3 154 683	47
Age group[a]			
<50	197 062	1 094 390	7
50–59	172 261	1 812 884	23
60–69	125 016	1 741 799	49
70+	30 188	956 958	54
Missing	3199	17	1
Country			
Mainland China, Singapore, Taiwan	241 764	2 134 363	52
Japan	251 409	3 253 033	76
Korea	34 553	218 652	6
Education[b]			
Low	192 514	2 156 352	58
Middle	215 396	2 230 623	38
High	49 202	441 066	10
Missing	70 614	778 007	28

[a]Number of subjects by age at baseline; person-years and cases are tabulated by attained age during follow-up.

[b]Low: no formal education or primary; middle: secondary or trade/technical; high: university or higher.

observation (average follow-up, 10.6 years). Women contributed 56% of person-years of observation; cohorts from Japan represented 58% of total person-years, those from mainland China, Singapore, and Taiwan, 38%. Thirty-seven percent of study subjects were ever smokers and 35% ever drinkers. A total of 134 cases of cancer of the small intestine were observed. Among them, 49 (37%) were classified as adenocarcinoma, 11 (8%) as carcinoid, 46 (34%) as neoplasms of other histologic types (consisting of 31 sarcomas, 9 lymphomas, 1 signet ring cell carcinoma, 1 squamous cell carcinoma *in situ*, 1 small cell carcinoma, and 3 carcinoma *in situ* NOS); histology was unknown for the remaining 28 (21%) cases.

The results of the analysis of the association between BMI and risk of small intestine cancer are reported in Table 2. There was a statistically non-significant trend toward an increased HR in subjects with BMI >25 kg/m^2. Results were comparable in men and women: specifically, the HR among subjects with BMI >27.5 kg/m^2 was 1.59 (95% CI 0.67–3.74) in men and 1.93 (0.72–5.20) in women (*P*-value of test of heterogeneity 0.77). The HR according to WHO categorization of BMI were 1.07 (95% CI 0.45–2.51), 1.12 (95% CI 0.68–1.83), 1 (reference group), 1.49 (95% CI 0.88–2.52), 0.39 (95% CI 0.53–2.91) for BMI <18.5, 18.5–22.99, 23.0–24.99 (reference group), and 30.0 +, respectively (*P* for trend 0.57). The results of the sensitivity analysis based on sex-specific quartiles of the BMI distribution were similar to those reported in Table 2 (not shown in detail).

The results of the analysis of tobacco smoking and alcohol drinking are presented in Table 3. Because only 8% of women were ever smokers and 16% were drinkers, compared with 70% and 56% among men, respectively, these results are restricted

Table 2. Hazard ratios of small intestine cancer for categories of body mass index (BMI)

BMI category	Cases	Person-years	HR (95% CI)
<20.0	15	876 448	0.87 (0.45–1.67)
20.1–22.5	43	1 525 375	1.47 (0.90–2.38)
22.6–25.0 (Reference)	33	1 704 332	1.00
25.1–27.5	23	914 013	1.49 (0.85–2.59)
27.6 +	15	512 143	1.50 (0.76–2.96)
Missing	5	73 737	N/A
P^*_{trend}			0.34

HR adjusted for age, sex, education, BMI and alcohol drinking.

*P-value of test for linear trend.

HR, hazard ratio; CI, confidence interval.

to men. No association was suggested with tobacco smoking: in particular, smokers of >40 pack-years had a statistically non-significantly lower risk of small intestine cancer, compared with never smokers. The analysis of alcohol drinking was hampered by the fact that 17% of person-years were accumulated by subjects with missing data on this risk factor. A statistically non-significant trend was observed between alcohol drinking and risk of small intestine cancer; in particular, subjects who reported drinking >400 g of ethanol per week (around five drinks per day) had an HR of 1.57 (95% CI 0.66–3.70).

The analysis of the combined risk score among men resulted in an HR of 1.40 (95% CI 0.60–3.27), 1.83 (95% CI 0.81–4.16), and 1.58 (95% CI 0.56–4.44) for combined scores of 1, 2, and 3, respectively.

In the stratified analysis, the results were very similar among Chinese (including mainland China, Singapore, and Taiwan) and Japanese (Korea was excluded from this analysis because of the small number of cases) for all three risk factors (results not reported in detail). The analysis of adenocarcinoma of the small intestine was limited by the small number of cases (49 in total): overall, these results were consistent with those that included all cases. In particular, the HR in the highest BMI category was 1.89 (95% CI, 0.63–5.68, based on five cases).

discussion

Our analysis of small intestine cancer in 12 cohorts from Asia provides some evidence of an etiologic role of obesity and heavy alcohol drinking in the etiology of this disease. These results are consistent with previous findings obtained from studies (mainly of case–control design) from the United States and Europe [22]. In this respect, the role of environmental factors in small intestine carcinogenesis resembles that which has been identified for the colorectum [23–25].

The interpretation of the evidence linking colorectal cancer with tobacco smoking remains controversial: in the latest Surgeon General Report on tobacco smoking, the evidence was considered suggestive of a causal association [26]. Furthermore, the evidence for an association of smoking with hyperplastic polyps, serrated polyps, and microsatellite instability (MSI)-high colorectal cancer is much more compelling than for colorectal cancer as a whole [27, 28]. Similar evaluations for

Downloaded from http://annonc.oxfordjournals.org/ at Fred Hutchinson Cancer Research Ctr on August 23, 2013

Table 3. Hazard ratios of small intestine cancer for tobacco smoking and alcohol drinking among men

Risk factor	Cases	Person-years	HR (95% CI)
Tobacco smoking			
Never smokers (Reference)	23	712 854	1.00
Ever smokers	62	1 711 906	1.18 (0.72–1.94)
Current smokers	44	1 313 990	1.17 (0.69–1.98)
Former smokers	18	397 737	1.20 (0.64–2.27)
Missing	2	26 605	N/A
Cumulative tobacco smoking			
0.1–20 pack-years	14	460 565	1.06 (0.52–2.17)
20.1–40 pack-years	32	685 250	1.60 (0.90–2.85)
>40 pack-years	12	469 709	0.70 (0.32–1.53)
Missing	4	96 382	N/A
P^{*}_{trend}			0.84
Alcohol drinking			
Never drinkers (Reference)	31	879 658	1.00
Ever drinkers	51	1 468 468	1.09 (0.67–1.76)
Missing	5	103 239	N/A
Average alcohol drinking			
0.01–100 g/week	19	476 889	1.23 (0.67–2.27)
100.1-400 g/week	16	475 862	1.19 (0.62–2.28)
>400 g/week	8	172 503	1.57 (0.66–3.70)
Missing	8	343 214	N/A
P^{*}_{trend}			0.30

HR, hazard ratio, adjusted for age, sex, education, body mass index and alcohol drinking.

*P-value of test for linear trend.

CI, confidence interval; HR, hazard ratio.

small intestine cancers have not been made. Our results, albeit limited by the small number of cases, support the hypothesis that tobacco smoking does not play a major role in the etiology of this neoplasm and that the positive results of previous case–control studies [9, 10, 11, 13, 15] may be due to selection or information bias or, perhaps, uncontrolled confounding with alcohol. Moreover, the risk estimates in previous studies did not suggest a role for quantity or duration of tobacco consumption, thus reducing the credibility of a causal association.

The suggestion of a carcinogenic effect of heavy alcohol drinking in cancer of the small intestine is consistent with the evidence of a similar effect in colorectal carcinogenesis [25]. An association between drinking of alcoholic beverages and increased risk of small intestine cancer has been reported in previous studies [9, 10, 13], with an approximate doubling of relative risk among heavy drinkers, similar to our findings. Other studies, however, did not confirm this association [11, 12]. Among the possible mechanisms of a carcinogenic effect of alcohol drinking on small intestine are a genotoxic effect of acetaldehyde, the main metabolite of ethanol; effects on DNA methylation perhaps via influences on folate metabolism; and alterations of immune response of the mucosa [25, 29].

Increased body mass is consistently linked to cancer of the colon, but the evidence for cancer of the small intestine is not consistent. In a cohort study of small intestine from Sweden, the relative risk for obese individuals was 2.8 (95% CI 1.6–4.5) [14]; while in a cohort study of USA Veterans, there was an association with obesity among white men but not among black men [16]. In a large cohort study of small intestine cancer from Norway, there was an increased risk associated with obesity in men, but not in women [17]. Other studies of obesity and cancer of the small intestine have shown either no association [12] or an inverse relationship with body mass [11]. Our results are compatible with a weak carcinogenic effect of BMI, but also with no effect; however, they certainly exclude a strong association between increased BMI and cancer risk.

We adopted a traditional frequentist approach to assess the statistical significance of our findings, and we were not able to reject the null hypotheses of no association between each of the three risk factors under study and the risk of small intestine cancer. In case of hypotheses that have been tested in previous studies, however, one could argue that a Bayesian approach is more appropriate to assess the marginal contribution of one specific finding to the overall evidence. This seems particularly relevant for rare outcomes and exposures, in which a frequentist approach might lead to an underestimate of the importance of findings and dismiss as 'non-significant'.

Limitations of our study included the lack of repeated measurements during follow-up, and the lack of validation of self-reported information on alcohol drinking and tobacco smoking: these are likely to result, if anything, in non-differential misclassification with respect to outcome. Thus, we cannot rule out the possibility that the weak associations we observed could be partly due to non-differential misclassification. The multicenter nature of the study might have resulted in lack of comparability of the results by cohort, which in turn should have resulted in underestimate of relative risks, because of the non-differential nature of this source of bias.

Strengths of the study were the prospective nature of the investigation, the low proportion of cohort members lost to follow-up, the relatively large number of cases (for this rare cancer), and the ability to stratify the results across countries at different levels of economic development.

In conclusion, our study offers some support to the hypothesis that elevated BMI is a risk factor of small intestine cancer. The results on tobacco smoking and alcohol drinking exclude a strong etiologic role of these habits. Our results are consistent with current evidence that the epidemiology of small intestine cancer resembles that of colorectal cancer. Assembling an even larger study sample should allow an improvement in the precision of the estimates of association.

funding

This work was supported by the National Cancer Institute at the National Institutes of Health (R03CA150038) and by the Fred Hutchinson Cancer Research Center. The original cohorts were supported by: Japan Public Health Center-based Study I & II (JPHC I & II): 1) Management Expenses Grants from the Government to the National Cancer Center; 2) Grant-in-Aid for Cancer Research from the Ministry of Health, Labour and Welfare, Japan; 3) Grant-in-Aid for the Third-Term Comprehensive Control Research for Cancer from the Ministry of Health, Labour and Welfare, Japan; Shanghai Women's Health Study (SWHS): United States Public Health Service

Downloaded from http://annonc.oxfordjournals.org/ at Fred Hutchinson Cancer Research Ctr on August 23, 2013

grant (R37CA070867); Singapore Chinese Health Study (SCHS): National Cancer Institute at the National Institutes of Health (R01CA55069, R35CA53890, R01CA90205, R01CA144034); Shanghai Men's Health Study (SMHS): United States Public Health Service grant (R01 CA082729); Radiation Effects Research Foundation (RERF): The Radiation Effects Research Foundation (RERF), Hiroshima and Nagasaki, Japan is a private, non-profit foundation funded by the Japanese Ministry of Health, Labour and Welfare (MHLW) and the U.S. Department of Energy (DOE), the latter in part through the National Academy of Sciences. This publication was supported by RERF Research Protocol RP-A03-10; Ohsaki National Health Insurance Cohort Study: Research Grant from Ministry of Health, Labour, and Welfare, Japan; Miyagi Cohort Study: Research Grant from Ministry of Health, Labour, and Welfare, Japan; Community-Based Cancer Screening Project (CBCSP): This work was supported by Health Promotion Bureau, Department of Health, Republic of China; Korea Multi-center Cancer Cohort (KMCC): Ministry of Education, Science and Technology, Korea (2009-0087452), National Research Foundation of Korea (2009-0087452); Shanghai Cohort Study (SCS): National Cancer Institute at the National Institutes of Health (R01CA43092, R01CA144034); National Cancer Center Screenee Cohort: Grants from the National Cancer Center, Korea (0910220); and Health Effects of Arsenic Longitudinal Study (HEALS): National Institutes for Health (P42ES010349, R01CA102484, R01CA107431).

disclosure

The authors declare no conflict of interest.

references

1. Sankaranarayanan R, Boffetta P. Research on cancer prevention, detection and management in low- and medium-income countries. Ann Oncol 2010; 21: 1935–1943.
2. Curado MP, Edwards B, Shin HR et al. Cancer Incidence in Five Continents Volume IX (IARC Scientific Publications No 160). Lyon, France: IARC 2007.
3. Parkin DM, Whelan SL, Ferlay J et al. Cancer Incidence in Five ContinentsVol. VIII (IARC Scientific Publications No. 155). Lyon, France: IARC 2002.
4. Bosman FT, Carneiro F, Hruban RH, Theise ND. Tumours of the small intestine. WHO Classification of Tumours of the Digestive System, 4th edition. Lyon, France: IARC 2010; 95–118.
5. Jess T, Gamborg M, Matzen P et al. Increased risk of intestinal cancer in Crohn's disease: a meta-analysis of population-based cohort studies. Am J Gastroenterol 2005; 100: 2724–2729.
6. Lok KH, Hung HG, Ng CH et al. The epidemiology and clinical characteristics of Crohn's disease in the Hong Kong Chinese population: experiences from a regional hospital. Hong Kong Med J 2007; 13: 436–441.
7. Yang SK, Yun S, Kim JH et al. Epidemiology of inflammatory bowel disease in the Songpa-Kangdong district, Seoul, Korea, 1986–2005: a KASID study. Inflamm Bowel Dis 2008; 14: 542–549.
8. Asakura K, Nishiwaki Y, Inoue N et al. Prevalence of ulcerative colitis and Crohn's disease in Japan. J Gastroenterol 2009; 44: 659–665.
9. 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: 205–207.
10. Wu AH, Yu MC, Mack TM. Smoking, alcohol use, dietary factors and risk of small intestinal adenocarcinoma. Int J Cancer 1997; 70: 512–517.
11. Negri E, Bosetti C, LaVecchia C et al. Risk factors for adenocarcinoma of the small intestine. Int J Cancer 1999; 82: 171–174.
12. Chow WH, Linet MS, McLaughlin JK. Risk factors for small intestine cancer. Cancer Causes Control 1993; 4: 163–169.
13. Kaerlev L, Teglbjaerg PS, Sabroe S et al. 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: 791–797.
14. Wolk A, Gridley G, Svensson M et al. A prospective study of obesity and cancer risk. Cancer Causes Control 2001; 12: 13–21.
15. Kaerlev L, Teglbjaerg PS, Sabroe S et al. The importance of smoking and medical history for development of small bowel carcinoid tumor: a European population-based case-control study. Cancer Causes Control 2002; 13: 27–34.
16. Samanic C, Gridley G, Chow WH et al. Obesity and cancer risk among white and black United States veterans. Cancer Causes Control 2004; 15: 35–43.
17. Bjorge T, Tretli S, Engeland A. Height and body mass index in relation to cancer of the small intestine in two million Norwegian men and women. Br J Cancer 2005; 93: 807–810.
18. Schatzkin A, Park Y, Leitzmann MF et al. Prospective study of dietary fiber, whole grain foods, and small intestinal cancer. Gastroenterol 2008; 135: 1163–1167.
19. Cross AJ, Leitzmann MF, Subar AF et al. A prospective study of meat and fat intake in relation to small intestinal cancer. Cancer Res 2008; 68: 9274–9279.
20. Zheng W, McLerran DF, Rolland B et al. Association between body-mass index and risk of death in more than 1 million Asians. N Engl J Med 2011; 364: 719–729.
21. Laird N, Olivier D. Covariance analysis of censored survival data using linear analysis techniques. JASA 1981; 76: 231–240.
22. Schottenfeld D, Beebe-Dimmer JL, Vigneau FD. The epidemiology and pathogenesis of neoplasia in the small intestine. Ann Epidemiol 2009; 19: 58–69.
23. Liang PS, Chen TY, Giovannucci E. Cigarette smoking and colorectal cancer incidence and mortality: systematic review and meta-analysis. Int J Cancer 2009; 124: 2406–2415.
24. Ning Y, Wang L, Giovannucci EL. A quantitative analysis of body mass index and colorectal cancer: findings from 56 observational studies. Obes Rev 2010; 11: 19–30.
25. Boffetta P, Hashibe M. Alcohol and cancer. Lancet Oncol 2006; 7: 149–156.
26. U.S. Department of Health and Human Services.The Health Consequences of Smoking: A Report of the Surgeon General Atlanta, GAU.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health 2004.
27. Morimoto LM, Newcomb PA, Ulrich CM et al. Risk factors for hyperplastic and adenomatous polyps: evidence for malignant potential?. Cancer Epidemiol Biomarkers Prev 2002; 11: 1012–1018.
28. Slattery ML, Curtin K, Anderson K et al. Associations between cigarette smoking, lifestyle factors, and microsatellite instability in colon tumors. J Natl Cancer Inst 2000; 92: 1831–1836.
29. Seitz HK, Stickel F. Molecular mechanisms of alcohol-mediated carcinogenesis. Nat Rev Cancer 2007; 7: 599–612.

Downloaded from http://annonc.oxfordjournals.org/ at Fred Hutchinson Cancer Research Ctr on August 23, 2013