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


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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/m², 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.
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 whole grain 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 alcohol: 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/m². The category 22.6–25.0 was chosen as reference, based on the results of a pooled 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/m²; 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
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/m². Results were comparable in men and women: specifically, the HR among subjects with BMI >27.5 kg/m² 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 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.

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

<table>
<thead>
<tr>
<th>BMI category</th>
<th>Cases</th>
<th>Person-years</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20.0</td>
<td>15</td>
<td>876 448</td>
<td>0.87 (0.45–1.67)</td>
</tr>
<tr>
<td>20.1–22.5</td>
<td>43</td>
<td>1 525 375</td>
<td>1.47 (0.90–2.38)</td>
</tr>
<tr>
<td>22.6–25.0 (Reference)</td>
<td>33</td>
<td>1 704 332</td>
<td>1.00</td>
</tr>
<tr>
<td>25.1–27.5</td>
<td>23</td>
<td>914 013</td>
<td>1.49 (0.85–2.59)</td>
</tr>
<tr>
<td>≥27.6</td>
<td>15</td>
<td>512 143</td>
<td>1.50 (0.76–2.96)</td>
</tr>
<tr>
<td>Missing</td>
<td>5</td>
<td>73 737</td>
<td>N/A</td>
</tr>
</tbody>
</table>

P<sub> trend </sub> = 0.34

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

HR, hazard ratio; CI, confidence interval.

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...
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.

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disclosure

The authors declare no conflict of interest.

references