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Lifestyle factors and small intestine adenocarcinoma risk: A systematic review and meta-analysis

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ABSTRACT

Background: Although the incidence of small intestinal adenocarcinoma (SIA) is low, rates are increasing and little information regarding modifiable lifestyle risk factors is available.
Aim: To provide a systematic review of lifestyle factors and SIA risk.
Methods: Ovid MEDLINE, EMBASE and Web of science were searched from inception to week 1 October 2013. Nine publications that reported on SIA risk in relation to alcohol intake ($n = 6$), tobacco smoking ($n = 6$), diet ($n = 5$), body mass ($n = 3$), physical activity ($n = 1$), hormone use ($n = 1$) and/or socio-economic status ($n = 3$) were retrieved. Results for alcohol, smoking and SIA risk were pooled using random-effects meta-analyses to produce relative risks (RR) and 95% confidence intervals (CI).
Results: The summary RR for individuals consuming the highest versus lowest category of alcohol intake was 1.51 (95% CI 0.83–2.75; $n = 5$ studies) with significant increased risks emerging in sensitivity analysis with reduced heterogeneity (RR: 1.82, 95% CI: 1.05–3.15; $n = 4$ studies). The pooled SIA RR for individuals in the highest versus lowest category of smoking was 1.24 (95% CI 0.71–2.17; $n = 5$ studies). In relation to dietary factors, high fibre intakes and normal body weight may be protective, while high intakes of red/processed meat and sugary drinks may increase SIA risk. Evidence on socio-economic status and SIA risk was equivocal. Data on other factors were too sparse to draw any conclusions.
Conclusions: Alcohol may be associated with an increased risk of SIA. Further investigation of lifestyle factors, particularly alcohol, smoking and diet, in the aetiology of this cancer is warranted in large consortial studies.

1. Introduction

The small intestine represents 75% of the length and 90% of the absorptive surface of the gastrointestinal system [1]. Despite its prime role in digestion, the small intestine is a relatively rare location for the development of neoplasms, accounting for only 2% of all gastrointestinal cancers, 0.4% of total cancer cases and 0.2% of all cancer deaths [2]. Worryingly though, the incidence of small intestine cancer increased substantially between 1973 and 2004 [3], and others have noted that this trend disproportionately affects Caucasian men [4]. This non-uniform increase across population groups suggests that the rise is not due to improved classification of tumour location, generating a need to better understand the causative factors of this malignancy.

Amongst the different histological types of small intestine cancer, small intestine adenocarcinoma (SIA), derived from mucosal gland epithelium, is amongst the most common [5]. It accounts for 50%, 20% and 15% of duodenal, jejunal and ileal cancers, respectively [3]. Clinical manifestations of SIA are usually non-specific and appear late in the disease, presenting a challenge for physicians, since patients often present with advanced cancer [6,7]. This late presentation is coupled with a poor prognosis for SIA, which currently has an overall 5-year survival rate of approximately 30% [8]. Therefore, in order to reduce future cancer burden, research emphasis must focus on preventative measures that may reduce SIA risk.

Abbreviations: BMI, body mass index; FFQ, food frequency questionnaire; HRT, hormone replacement therapy; SIA, small intestine adenocarcinoma; HNPCC, hereditary nonpolyposis colorectal cancer.

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Certain medical conditions, including hereditary nonpolyposis colorectal cancer (HNPCC), Peutz-Jeghers syndrome and Crohn's disease have been established as risk factors for SIA [6,9–14]. However, little is known about modifiable lifestyle factors that may be related to SIA, even though such factors are of considerable aetiological importance for other tumours of the gastrointestinal tract [15,16]. The purpose of this article is to conduct a novel systematic review, and meta-analyses where possible, evaluating the association between lifestyle factors and SIA development.

2. Methods

2.1. Search strategy

The bibliographic databases Ovid MEDLINE (US National Library of Medicine, Bethesda, Maryland), EMBASE (Reed Elsevier PLC, Amsterdam, Netherlands) and Web of Science (Thompson Reuters, Times Square, New York, USA) were searched from inception to week 1 October 2013 for literature related to lifestyle factors and SIA risk. The search strategy identified studies that contained at least one keyword or Medical Subject Heading (MeSH) term from each of the following:

(i) risk factor(s) or alcohol drinking or alcohol consumption or diet or nutrition or smoking or body mass index or BMI or occupation(s) or socioeconomic status or physical activity or exercise or radiation injuries or radiation induced neoplasm(s) or environmental exposure or occupational exposure or obesity or medication or hormone replacement therapy or reproductive factors and
(ii) small intestine adenocarcinoma or small bowel adenocarcinoma or small intestine cancer or small bowel cancer or duodenal neoplasms or ileal neoplasms or jejunal neoplasms

The search strategy also incorporated limits to studies conducted on humans. Case studies, case series and review articles were removed, however no language restrictions were specified.

2.2. Data extraction

Titles and abstracts were independently examined by at least two reviewers (CB, HC, PV, MC, CL &/or LM) to assess eligibility for the review using 'PICO' criteria:

(i) Participants: males and females, no age restrictions
(ii) Intervention: assessment of lifestyle factors in the study population
(iii) Comparators: healthy individuals with no small intestine cancer
(iv) Outcome: small intestine adenocarcinoma risk
(v) Study design: observational including cohort and case–control studies.

The reviewers initially screened titles and abstracts to remove obviously irrelevant articles, and then at least two reviewers (CB, BSc Hons, HC, PhD BSc Hons, and/or PV, MB BCh BSc MPH) screened full text articles independently to identify studies for inclusion in the systematic review. Discrepancies were resolved by discussion. Reference lists of included articles were also searched for other relevant studies. Since this systematic review focuses on SIA risk, studies were excluded if they presented data on small intestine cancer as one entity, or if they only presented data on small intestine sarcoma, small intestine lymphoma or small intestine neuroendocrine/carcinoid tumours. Studies that reported small intestine cancer as one entity were contacted to retrieve SIA specific data. Methodological quality was evaluated using the Newcastle-Ottawa Scale [17] to assess the selection of the study groups (0–4 points); the comparability of the groups (0–2 points); and the ascertainment of the exposure or outcome of interest (0–3 points).

2.3. Narrative synthesis and statistical analysis

Following critical review of each study, a narrative synthesis was compiled. Where possible, the association between cancer risk and lifestyle factors was summarised in meta-analyses by comparing risk in the highest to the lowest reported category of exposure. Adjusted relative risk estimates (RR) and their corresponding 95% confidence intervals (CI) were extracted from published reports for each study. In case–control studies adjusted odds ratios (OR) were used, whereas adjusted hazard rate ratios (HR) were extracted from cohort studies, both of which should approximate RR since SIA is extremely rare [18]. Random-effects models were used to calculate pooled RR and the I^2 statistic [19] was calculated to quantify the degree of heterogeneity between studies. Study specific weights in the random-effects model were calculated and scaled to percentages. An a priori decision was made to perform meta-analyses only for lifestyle risk factors that were investigated by at least three published studies. This meant that meta-analyses were possible for alcohol and smoking as risk factors for SIA. Publication and selection bias were investigated by checking for asymmetry in the funnel plots of the study RR against the standard error of the logarithm of the RR [20]. Sensitivity analyses were performed for alcohol and smoking meta-analyses by systematically removing each individual study in order to assess its effect on the pooled result estimates and accompanying heterogeneity. Statistical analysis was conducted using the metan package in Intercooled STATA version 11.2 (StataCorp 2005, College Station, TX, USA).

3. Results

As shown in Fig. 1, screening of the 2319 papers identified in our search strategy resulted in nine publications [21–29] deemed eligible for inclusion in the review. The characteristics of these are summarised in Table 1 and consist of four studies from prospective cohorts or consortiums [21,23,24,28], two population-based case–control studies [25,29] and three hospital-based case–control studies [22,26,27]. These studies, of variable quality, originated from America, Europe and a large Asian Cohort Consortium (Table 1).

3.1. Alcohol

Four case–control studies and one cohort study examined alcohol consumption and SIA risk [22,23,26,27,29]. As shown in Fig. 2, the pooled RR for those consuming the highest versus lowest category of alcohol intake was 1.51 (95% CI: 0.83–2.75) with heterogeneity of 61.4%. Sensitivity analysis significantly altered the results shown with the removal of the Negri et al. study [27], making the pooled RR 1.82 (95% CI: 1.05–3.15) and a reduced heterogeneity of 28.0% (Fig. 3). Removal of other studies in sensitivity analysis did not markedly alter the results shown, or accompanying heterogeneity (Table 2). In addition, Kaerlev et al. [26] investigated specific alcoholic drinks and observed significant increased risks of SIA for heavy consumers ($\geq$25 g alcohol/day) of beer (OR 3.5; 95% CI: 1.5–8.0) and spirits (OR 3.4; 95% CI: 1.3–9.2) but not wine. Contrastingly, no links between differing alcohol types and SIA risk was observed in an American case–control study [29].

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