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Pernicious anemia and colorectal cancer risk – A nested case–control study

Ben Boursi[a,b,c,e], Ronac Mamtani[b,c,d], Kevin Haynes[b,c], Yu-Xiao Yang[a,b,c,*]

[a] Division of Gastroenterology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA
[b] Center for Clinical Epidemiology and Biostatistics, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA
[c] Department of Biostatistics and Epidemiology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA
[d] Division of Hematology/Oncology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA
[e] Tel-Aviv University, Tel-Aviv, Israel

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ABSTRACT

Background: Hypergastrinemia was shown to stimulate colonic epithelial cell proliferation.
Aims: To evaluate the association between pernicious anemia (PA), a disease with hypergastrinemia, and colorectal cancer (CRC) risk.
Methods: We conducted a nested case–control study within a large database from the UK. Cases were defined as all individuals in the cohort with at least one medical code for CRC. Controls were selected based on incidence-density sampling. For each case, up to four eligible controls were matched on age at diagnosis, sex, practice-site, and both duration and calendar time of follow-up. Exposure of interest was diagnosis of PA prior to CRC diagnosis date. The primary analysis was a multivariable conditional logistic regression.
Results: Our study included 22,098 CRC cases and 85,969 matched controls. We identified 154 (0.70%) cases and 563 (0.65%) controls with past history of PA. The adjusted OR for the association between PA and CRC risk was 1.02 (95% CI 0.85–1.22). There was no difference in the results after stratification according to sex. In a sensitivity analysis only among individuals without chronic use of proton pump inhibitors (PPIs) the adjusted OR was 1.14 (95% CI 0.90–1.45). There was no association between duration of PA and CRC risk.
Conclusion: PA is not associated with higher CRC risk.
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1. Introduction

Pernicious anemia is a chronic auto-immune disease characterized by destruction of parietal cells in the fundus and body of the stomach. The estimated disease prevalence is 0.1% in the general population and 1.9% among adults more than 60 years old. A female predominance of 1.5:1 was described in the UK and Scandinavia, however data from the US show equal sex distribution [1–4]. The parietal cells are responsible for both the secretion of gastric acid through the H^+/K^+ ATPase as well as intrinsic factor, thus loss of these cells leads to achlorhydria and megaloblastic anemia secondary to lack of absorption of ingested vitamin B12 [1–3].

Hypergastrinemia has been identified in patients with pernicious anemia as a physiologic response to the damage to the oxyntic mucosa and achlorhydria. However, beyond the role of gastrin in gastric acid secretion, it was also shown to stimulate the growth of epithelial cells and prevent apoptosis [5–9]. Gastrin and its precursors activate several pathway important in tumorigenesis such as the beta catenin, MAP kinase and JAK2/STAT3 pathways and were described in association with stomach, colorectal, pancreatic and liver cancers as well as carcinoids [5,6,10–18].

In animal models of colon cancer, chronic hypergastrinemia was shown to act as a co-carcinogen that can increases disease risk in susceptible $APC^{Min-/+}$ animals or following azoxymethane administration [19–21]. In humans, gastrin at physiological concentrations was shown to act as a growth factor for colorectal cancer (CRC) both through endocrine as well autocrine/paracrine mechanisms and pre malignant adenomas were also shown to express an isoform of the cholecystokinin B/gastrin receptor [22–24].

Epidemiological studies to date had shown conflicting results regarding the association between pernicious anemia and CRC.

* Corresponding author at: Division of Gastroenterology, Department of Medicine, Center for Clinical Epidemiology and Biostatistics, Perelman School of Medicine at the University of Pennsylvania, 733 Blockley Hall, 423 Guardian Drive, Philadelphia, PA 19104-6021, USA. Fax: +1 215 349 5915.
E-mail address: yangy@mail.med.upenn.edu (Y.-X. Yang).

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The sample size in most of those studies was small and several important risk factors for CRC, such as obesity, smoking history, alcohol consumption, diabetes, chronic aspirin/NSAIDs use, HRT and previous colonoscopies were not adjusted for [15,25–28]. Of note, additional studies among patients with other disease states associated with hypergastrinemia, such as the Zollinger–Ellison syndrome and chronic use of proton pump inhibitors (PPIs) have not demonstrated elevated CRC risk [29–31].

The aim of the current study was to evaluate the association between pernicious anemia and CRC risk in a large population representative database adjusted to common CRC risk factors as well as PPI use.

2. Methods

2.1. Data source

The Health Improvement Network (THIN) is a large population representative database from the United Kingdom (UK) [32]. The database contains comprehensive medical records of more than 10 million individuals treated by general practitioners in 570 practices throughout the UK. THIN is designed to serve research purposes. All practices contributing data to THIN follow a standardized protocol of entering information and transmitting information to the central database. Each medical diagnosis is defined using Read diagnostic codes, the standard clinical terminology system used in general practices in the UK [33,34]. Data quality is monitored through routine analysis of the entered data [35]. Previous studies demonstrated that the incidence of CRC in THIN was comparable to the incidence in the entire population of the UK as reported in cancer registry data [36].

2.2. Study design and population

We conducted a nested case–control study with incidence density sampling of controls. This design yields odds ratios (ORs) that are statistically unbiased estimates of the incidence rate ratio [37]. All individuals receiving medical care from 1995 to 2013 from a THIN practitioner were potentially eligible for inclusion. Subjects with a history of familial CRC syndromes or inflammatory bowel disease (IBD) were excluded in order to focus on population at average risk for CRC. Follow-up started at the later of either the date when the THIN practice started using the electronic medical record software or 183 days after the date at which the patient registered with their general practitioner, and ended on the CRC diagnosis date for those diagnosed with CRC during the follow-up and on the earliest of date of death, transferring out of the database, or reach the end date of the database for controls. The study was approved by the Institutional Review Board at the University of Pennsylvania and by the Scientific Review Committee of THIN.

2.3. Case selection

Cases were defined as all individuals in the cohort that were given at least one medical Read code for CRC during the follow-up period and were more than 40 years old at the time of diagnosis. Subjects who were diagnosed within the first 6 months after initiation of follow-up were excluded in order to avoid prevalent cases [38]. Index date was defined as the date of first CRC diagnosis.

2.4. Selection of controls

Selection of the controls was based on incidence density sampling [37,39]. The eligible control pool for each case comprised of all individuals without a diagnosis of CRC at the date the case was diagnosed. For each case, up to four eligible controls were matched on age at index date (±5 years), sex, practice site, and both duration and calendar time of follow-up. Controls were assigned the same index date as their matched cases.

2.5. Exposures and covariates

The primary exposure of interest was diagnosis of pernicious anemia prior to CRC diagnosis date, using four different models. In the first model (model 1) pernicious anemia was defined as all individuals with the specific pernicious anemia Read code "D010.00"; in the second model (model 2) at least 1 year of therapy with vitamin B12 was required in addition to a diagnostic code for pernicious anemia; in the third model (model 3) we further required cases to have no previous prescriptions with proton pump inhibitors (PPIs) that are known to increase gastrin levels; and in the fourth model (model 4) we added the requirement of at least six months between registration date and pernicious anemia diagnosis in order to avoid prevalent cases. As possible confounders, we evaluated known risk factors for CRC, including obesity (defined as BMI > 30), smoking history (ever/never), alcohol consumption (any use and alcoholism/alcohol dependence), diabetes mellitus, previous screening colonoscopy (>2 years before index date), use of hormone replacement therapy (HRT), and chronic use of aspirin/NSAIDs (defined as first Prescription at least one year before index date). All covariates were evaluated before index date.

2.6. Statistical analysis

We compared the baseline characteristics of cases and controls using chi square tests for categorical variables and *t*-tests for continuous variables. The primary analysis was a multivariable conditional logistic regression to estimate odds ratios (ORs) and 95% confidence interval for the association between pernicious anemia and CRC risk. The analysis was adjusted to all of the above covariates. We also repeated the analysis after stratification according to sex. Since PPIs are also known to be associated with secondary hypergastrinemia [31], we performed a sensitivity analysis evaluating the risk in both cases and controls without chronic PPI use (defined as all individuals with first prescription more than one year before index date). In addition, we analyzed the association between duration of pernicious anemia and CRC risk. All calculations were done using STATA 13.

3. Results

The study population consisted of 22,163 sporadic CRC patients and 86,538 matched controls. Of them 65 cases and 569 controls with a diagnosis of pernicious anemia after index date were excluded. The median duration of follow-up before index date was 6.2 years (SD 4.1). Characteristics of cases and controls are presented in Table 1. Cases were more likely to be obese, ever smokers or have a past medical history of diabetes mellitus. Controls were more likely to have a history of screening colonoscopy.

We identified in our cohort 717 subjects (0.66%) with at least one Read code for pernicious anemia before index date. Among them, 154 (0.70%) were CRC cases and 563 (0.65%) were controls. There was no association between past history of pernicious anemia and CRC risk with unadjusted OR of 1.04 (95% CI 0.87–1.25) and adjusted OR of 1.02 (95% CI 0.85–1.22) (Table 2). There was no difference in the results after stratification according to sex. The adjusted OR was 0.96 (95% CI 0.73–1.26) for males and 1.07 (95% CI 0.84–1.36) for females (Table 3). When the characteristics of males and females were compared females were older (72.1 vs. 70.3 respectively) and more likely to be obese (18.4% vs. 19.5% respectively) while males

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