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Meta-Analysis

# Incidence of cancer (other than gastric cancer) in pernicious anaemia: A systematic review with meta-analysis

Edith Lahner*, Marina Capasso, Marilia Carabotti, Bruno Annibale

*Medical-Surgical Department of Clinical Sciences and Translational Medicine, Sapienza University of Rome, Italy*

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ABSTRACT

*Background:* Pernicious anaemia (PA) is associated with increased gastric cancer risk, but the evidence is conflicting regarding the associated risk of other cancers.
*Aim:* To systematically determine the incidence rates of gastro-intestinal cancers other than gastric cancers (GI-other-than-GC) and non-gastrointestinal cancers (non-GIC) in PA adults, globally and per tumour site, and the risk associated with PA for GI-other than GC and non-GIC.
*Methods:* Studies of PA patients reporting the incidence of GI-other-than-GCs and non-GICs were identified with MEDLINE (PubMed)-EMBASE (from first date available to April 2017). A meta-analysis of annual cancer incidence rates was performed. The outcome was the cumulative incidence of GI-other-than-GCs and non-GICs (ratio between the numbers of new cancer cases identified during the follow-up period and the number of PA patients) and the incidence rate expressed as the rate of events-per-time-unit (person-years).
*Results:* Of 82,257 PA patients, the pooled incidence rates/100 person-years for non-GCs and non-GICs of 0.27 (95% CI:0.16–0.42) and 0.23 (95% CI:0.22–0.25) were calculated by meta-analysis. Compared to the GLOBOCAN data for the general population from the countries of the included studies, the meta-analysis showed an overall relative risk (RR) of cancer in PA of 0.68 (95% CI:0.48–0.95). PA patients had a lower RR of colorectal, breast, liver, oesophageal, lung, thyroid, ovary, non-melanoma skin and kidney cancers but had a higher RR of biliary tract cancer (1.81:1.21–2.70), multiple myeloma (2.83:1.76–4.55), Hodgkin's lymphoma (3.0:1.35–6.68), non-Hodgkin's lymphoma (2.08: 1.58–2.75), and leukaemia (1.56:1.16–2.12).
*Conclusion:* An overall lower RR of cancers-other-than-gastric-cancer in PA patients but an increased RR of biliary tract cancers and haematological malignancies was observed.


## 1. Introduction

Pernicious anaemia (PA) is a macrocytic anaemia that results from cobalamin deficiency due to intrinsic factor deficiency, a protein avidly bound to dietary vitamin $B_{12}$ that promotes its transport to the terminal ileum for absorption. Intrinsic factor deficiency is due to the presence of atrophic gastritis (AG), resulting in the loss of oxyntic mucosa and parietal cells and therefore the lack of chlorhydric acid as well as intrinsic factor secretion [1,2]. PA is considered a late stage of autoimmune gastritis, and it is often associated with positivity to parietal cell and/or intrinsic factor autoantibodies and with the presence of other autoimmune disorders, usually autoimmune thyroid disease, type I diabetes, or vitiligo [3,4].

Similar to other autoimmune diseases, PA has been associated with an increased risk of cancer development [5]. A systematic review revealed a pooled gastric cancer incidence rate in PA patients of 0.3/100 person-years and an estimated 7-fold relative risk of gastric cancer [6]. In AG patients, type 1 gastric carcinoids may also occur [7–9]. High serum gastrin levels are found in PA as a response to damaged oxyntic mucosa and impaired gastric acid secretion. Hypergastrinaemia was shown to stimulate the growth of epithelial cells and to prevent apoptosis, possibly contributing to increased cancer risk [10]. In addition to gastric cancer and type 1 gastric carcinoids, PA has also been reported to be associated with an increased risk of cancers other than gastric neoplasias. Prior studies evaluating the possible association of PA with cancer risk have resulted in conflicting evidence; population-based studies mainly reported an increased odds ratio

* Corresponding author at: Sapienza University of Rome, Department of Medical-Surgical Sciences and Translational Medicine, Via Grottarossa 1035, 00189 Rome, Italy.
*E-mail address:* edith.lahner@uniroma1.it (E. Lahner).

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for haematological malignancies, such as monoclonal gammopathy of undetermined significance (MGUS) [11], multiple myeloma [12–14], acute myeloid leukaemia [14,15], chronic lymphocytic leukaemia [16], and myelodysplastic syndrome [14,15]. In contrast, a case-control study did not observe an association between PA and haematological malignancies [17]. Murphy et al. recently reported that patients with PA seem to be at increased risk for tonsillar cancer (OR 2.18), hypopharyngeal cancer (OR 1.92), oesophageal squamous cell carcinoma (OR 2.12), small intestinal cancer (OR 1.63) and liver cancer (OR 1.49) [14].

The aim of the present study was to determine the incidence rates of gastro-intestinal cancers other than gastric cancers (GI-other than GC) and non-gastrointestinal cancers (non-GIC) in adult patients with PA, both globally and per tumour site, and to determine the risk associated with PA for GI-other than GC and non-GIC by systematically reviewing the literature.

## 2. Methods

### 2.1. Literature search strategy

The literature on adult PA patients and the development of GI-other than GC and non-GIC was systematically reviewed. The search was conducted according to PRISMA guidelines [18]. The electronic databases MEDLINE (PubMed) and EMBASE were systematically searched combining the main keywords “pernicious anaemia”; “autoimmune gastritis”; and “cancer”.

The search was translated into the following query: (“pernicious anaemia”[All Fields] OR “anaemia”, “pernicious”[MeSH Terms] OR (“anaemia”[All Fields] AND “pernicious”[All Fields]) OR (autoimmune[All Fields] AND (“gastritis”[MeSH Terms] OR “gastritis”[All Fields]) AND (“neoplasms”[All Fields] OR “cancer”[All Fields]) OR “carcinoma”[All Fields]) AND (“humans”[MeSH Terms] AND (English[lang] OR French[lang] OR German[lang] OR Spanish[lang]).

No publication date restrictions were imposed. Reports published in English, German, French, Italian, and Spanish were considered.

### 2.2. Study selection

Studies published from the first date available up to April 27th, 2017 were included in the systematic review if they fulfilled all of the following criteria: (1) an observational study including patients with PA and reporting the numbers of non-gastric and/or non-GI cancers identified during a defined follow-up period; (2) a study performed in adult patients; and (3) a study with an original full paper that presented unique data. Studies were excluded if (1) they were reviews, letters, editorials, or case-reports and (2) follow-up data were not available.

Potentially relevant articles were screened for eligibility independently in an unblinded, standardized manner by the two reviewers (EL, MC), first by the abstract and then by the full text when necessary to determine whether they met the inclusion criteria. Disagreement between reviewers was resolved by discussion. The reference lists of the identified articles and relevant reviews were manually searched for additional studies that may have been missed using the electronic search strategy.

### 2.3. Data extraction

Two reviewers (EL, MC) independently extracted the following information from each publication: name of the first author, publication year, country of study location, study design, criteria for diagnosis of PA, sources of participant selection, numbers of investigated patients, duration of follow-up period (expressed in years), calculation of person-years (PY), age of patients (median or mean or range), gender, methods for identification of cancer, type of cancers, and numbers of cancer cases.

### 2.4. Outcome

The outcome measures of interest were the cumulative incidence of GI-other than GCs and non-GICs, calculated as the ratio between the numbers of new cancer cases identified during the follow-up period and the number of PA patients, and the incidence rate was expressed as a rate of events per unit of time (person-years).

### 2.5. Statistical analyses

From each included study, the number of incident non-GC and non-GIC cases and the number of PA patients exposed to risk were extracted. The cumulative incidence and the PY incidence rates in PA patients were calculated by the reviewers, if not explicitly stated.

The cumulative incidence was calculated as the ratio between new non-GC and non-GIC cases and the number of PA patients. The PY incidence rates were calculated as the ratio between new non-GC and non-GIC cases and PY. The weighted summary proportion (pooled proportion) under the fixed and random effects model were calculated by a Freeman–Tukey transformation for all the non-GC and non-GIC cases and were calculated separately for specific cancer sites in single systems or organs. In the case of a positive “heterogeneity test” ($p$-value < 0.10), the more appropriate random effects model was taken into consideration, in which both the random variation within the studies and the variation between the different studies was incorporated [19]. The extent of heterogeneity was investigated using Cochran’s Q and $I^2$ statistic [20]. The pooled incidence rates derived by meta-analysis were then compared with the annual cancer incidence rates of both genders in the general population aged over 40 years, as reported for the single European countries by the website GLOBOCAN (taking into consideration those countries to which the single studies included in the meta-analysis refer to) [21] by the Mantel–Haenszel method for calculating the weighted summary relative risk under the fixed effects model and the random effects model [19]. The statistical analysis was carried out using a dedicated software package (MedCalc Software, Mariakerke, Belgium, version 12.7.8.0).

### 2.6. Quality assessment

The quality of all the included studies was evaluated based on the Newcastle-Ottawa quality assessment scale [22]. This scale awards a maximum of nine stars to each study. Three categories are considered: (i) cohort selection including four items, (ii) outcome assessment with three items, and (iii) comparability between cohorts and controls with two items. A study can be awarded a maximum of one star for each numbered item within the selection and outcome assessment categories and two stars for comparability. Studies were defined as of high quality when they obtained nine stars, of medium quality when they obtained seven or eight stars, of low quality when they obtained five or six stars, and of very low quality when they obtained four stars or less. Discrepancies in quality assessment were discussed and resolved by two reviewers (EL, MC).

## 3. Results

### 3.1. Search results

The electronic search strategy identified a total of 2243 records from electronic databases and manual searches of the reference

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