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# Tobacco smoking and intestinal metaplasia: Systematic review and meta-analysis

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ABSTRACT

*Background:* The evaluation of specific risk factors for early endpoints in the gastric carcinogenesis pathway may further contribute to the understanding of gastric cancer aetiology.
*Aims:* To quantify the relation between smoking and intestinal metaplasia through systematic review and meta-analysis.
*Methods:* Articles providing data on the association between smoking and intestinal metaplasia were identified in PubMed®, Scopus® and Web of Science™, searched until April 2014, and through backward citation tracking. Summary odds ratio estimates and 95% confidence intervals were computed using the DerSimonian and Laird method. Heterogeneity was quantitatively assessed using the $I^2$ statistic.
*Results:* A total of 32 articles were included in this systematic review and 19 provided data for meta-analysis. Smoking was defined as ever vs. never (crude estimates, six studies, summary odds ratio = 1.54, 95% confidence interval: 1.12–2.12, $I^2$ = 67.4%; adjusted estimates, seven studies, summary odds ratio = 1.26, 95% confidence interval: 0.98–1.61, $I^2$ = 65.0%) and current vs. non-smokers (crude estimates, seven studies, summary odds ratio = 1.27, 95% confidence interval: 0.88–1.84, $I^2$ = 73.4%; adjusted estimates, two studies, summary odds ratio 1.49, 95% confidence interval: 0.99–2.25, $I^2$ = 0.0%).
*Conclusion:* The weak and non-statistically significant association found through meta-analysis of the available evidence does not confirm smoking as an independent risk factor for intestinal metaplasia.


## 1. Introduction

Gastric cancer is the fifth most common malignancy in the world and the third leading cause of cancer mortality worldwide [1]. Incidence and mortality rates have been diminishing for several decades [2,3], mostly due to the decrease in the frequency of cancers of the "intestinal" histological type [4,5], which account for approximately up to three-quarters of the total [4,6–9]. However, recent trends show that in some countries the declines are becoming less marked [3].

It is widely accepted that intestinal type gastric carcinomas are preceded by atrophic gastritis, intestinal metaplasia (IM), and dysplasia, following a set of sequential steps, known as Correa's cascade [10]. Although *Helicobacter pylori* infection plays an essential role in this process, other environmental exposures are needed for the progression towards cancer [11]. The evaluation of specific risk factors for early endpoints in the gastric carcinogenesis pathway may further contribute to the understanding of gastric cancer aetiology.

Gastric cancer is now considered a tobacco-related cancer [12,13]; current smokers were estimated to have a higher risk of gastric cancer when compared to never smokers (summary relative risk estimates: 1.62 in men and 1.20 in women) [14,15]. The associations are lower when comparing former and never smokers (summary relative risk estimates: 1.34 in men and 1.16 in women) suggesting smoking cessation leads to a reduction in risk [16]. The relation between smoking and precancerous lesions, especially IM, has been extensively studied [17]; however, to our knowledge, no meta-analyses of studies quantifying this association are available.

We aimed to quantify the relation between tobacco smoking and IM through systematic review and meta-analysis of the published epidemiological evidence.

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## 2. Materials and methods

A study protocol was predefined by the authors and followed throughout the review.

### 2.1. Search strategy

PubMed®, Scopus® and Web of Science™ were searched, from inception to April 2014, to identify published articles evaluating the relationship between tobacco smoking and IM, with no language restrictions; the search expressions are provided in the PRISMA systematic review flowchart (Fig. 1). The list of bibliographic references of the original reports considered eligible for the systematic review and review articles on these topics were also screened.

### 2.2. Selection of the studies

The list of references was independently screened by three reviewers (SM, SR and LA), in three consecutive steps, applying predefined criteria. In the first step, studies were excluded considering only information presented in the title and abstract. In the second step, full texts of articles not previously excluded were assessed to determine their eligibility for the systematic review. In the last step, full texts were re-evaluated to determine eligibility for meta-analysis.

Published articles were included when all of the following criteria were met: (1) original reports of case–control or cross-sectional studies, including baseline evaluations of randomized clinical trials or cohort studies; (2) articles addressing the association between tobacco smoking and the occurrence of IM in human adults; (3) exposure defined as smoking cigarettes, pipes, bidis or cigars; and (4) outcome defined as intestinal metaplasia of the stomach, excluding the cardia, as this is a more heterogeneous condition that may follow the aetiology of oesophageal more closely than that of gastric cancer [18–20]. Among reports with overlapping samples, we selected those providing data regarding the largest number of cases or presenting more detailed information regarding tobacco exposure.

The decisions taken independently by the reviewers in each step were compared and discrepancies were resolved by consensus, or involving a fourth researcher (BP or NL).

### 2.3. Data extraction and meta-analysis

We extracted data on the following items: publication year; country where the sample was assembled; selection of the participants and sample size; number of biopsy fragments and criteria used for the diagnosis of IM; odds ratio (OR) estimates and corresponding 95% confidence intervals (95% CI), or the necessary information to compute them, for the association between smoking and IM; control for potential confounding factors.

When a study provided OR estimates adjusted for a different number of potential confounders, the one adjusted for the largest number of variables was selected. For studies providing adjusted estimates only for the relation between exposures other than smoking and IM, crude estimates for the association between smoking and IM were computed if sufficient data was available. Lastly, if only crude estimates or the necessary information to compute them were available, these were extracted.

When data regarding IM in different stomach locations were presented separately, the measures referring to antrum were selected for meta-analyses, as this better reflects the more frequent location of adenocarcinomas, specially of the intestinal type [20–23].

Data extraction was performed independently by two researchers (SM and SR) and disagreements were resolved by consensus, or involving a third researcher (BP or NL).

We conducted meta-analyses for the association between smoking (ever vs. never and current vs. non-smokers) and IM. The DerSimonian and Laird method was used to compute summary OR estimates, and respective 95% CI. Heterogeneity was quantified using the $I^2$ statistic [24]. Visual inspection of the funnel plots and the Egger's regression asymmetry test were used for assessment of publication bias [25]. Sensitivity analyses were carried out taking different inclusion criteria into account, as described in the footnotes of the forest plots used to summarize the results.

The statistical analysis was performed with STATA®, version 11 (STATA Corp., College Station, TX, USA).

## 3. Results

### 3.1. Systematic review

Thirty-two articles were included in the systematic review (Supplementary Tables S1 and S2). Fifteen studies were conducted in Asia [26–40] (five from Japan, four from China, three from Korea, two from Iran and one from Taiwan), eight in Europe [41–48] (a multicentre study and one each from England, Finland, Italy, Netherlands, Poland, Portugal and Spain), four in North America [49–52] (participants were Asian/Hawaiian in two of them), three in South America [53–55] (Venezuela, Peru and El Salvador) and one each in Oceania [56] (New Zealand) and in Africa [57] (Mozambique).

Seventeen studies [27,28,30–33,40,41,43,44,46–52,56,57] recruited only patients referred due to gastrointestinal complaints. Twelve study populations [26,29,35–37,39,45,53–55] included volunteers from community screening programmes. Two studies [38,42] included participants referred due to gastrointestinal complaints as well as volunteers, and one study [34] recruited first-degree relatives of gastric cancer patients.

The number of biopsies performed for histological diagnosis ranged between two and 14 (Supplementary Tables S1 and S2); however, three articles [36,49,51] did not provide information on the number of biopsies. Only 15 studies specified the classification system used to assess IM; from these, 13 studies [11,27,30–32,34,35,37,38,43,44,47,48] used the Updated Sydney System.

### 3.2. Meta-analyses

A total of 19 articles [28–30,32–38,42,48,50–56] provided quantitative information on the relation between tobacco smoking and IM, most of them following a cross-sectional evaluation of the participants (17 cross-sectional, from which six were a baseline evaluation of a cohort and one a baseline evaluation of a randomized controlled trial) and five were case–control studies (Supplementary Table S1).

#### 3.2.1. Ever vs. never smokers

A total of 13 studies [28,29,32,33,35–37,42,48,50,51,53,55], evaluating 3410 IM patients and 8630 controls, classified smoking exposure as ever vs. never (Fig. 2). The combined OR estimate for the association between ever smoking and IM was 1.54 (95% CI: 1.12–2.12, $I^2 = 67.4\%$) for crude estimates, and 1.26 (95% CI: 0.98–1.61, $I^2 = 65.0\%$) when considering only the seven studies providing adjusted OR estimates. The results remained essentially unchanged when sensitivity analyses were conducted (Fig. 2).

Visual inspection of the funnel plot for ever vs. never smoking (Fig. 4) suggested an underrepresentation of small studies with