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# Occupational Exposures and Odds of Gastric Cancer: A StoP Project Consortium Pooled Analysis

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## Abstract

**Background:** Gastric cancer pathogenesis represents a complex interaction of host genetic determinants, microbial virulence factors, and environmental exposures. Our primary aim was to determine the association between occupations/occupational exposures and odds of gastric cancer.

**Methods:** We conducted a pooled-analysis of individual-level data harmonized from 11 studies in the Stomach cancer Pooling Project. Multivariable logistic regression was used to estimate the odds ratio (OR) of gastric cancer adjusted for relevant confounders.

**Results:** A total of 5279 gastric cancer cases and 12,297 controls were analyzed. There were higher odds of gastric cancer among labor-related occupations, including: agricultural and animal husbandry workers (OR 1.33, 95% CI:1.06–1.68); miners, quarrymen, well-drillers and related workers (OR 1.70, 95% CI:1.01–2.88); blacksmiths, toolmakers and machine-tool operators (OR 1.41, 95% CI:1.05–1.89); bricklayers, carpenters and construction workers (OR 1.30, 95% CI:1.06–1.60); and stationary engine and related equipment operators (OR 6.53, 95% CI:1.41–30.19). The ORs for wood-dust exposure were 1.51 (95% CI:1.01–2.26) for intestinal-type and 2.52 (95% CI:1.46–4.33) for diffuse-type gastric cancer. Corresponding values for aromatic amine exposure were 1.83 (95% CI: 1.09–3.06) and 2.92 (95% CI:1.36–6.26). Exposure to coal derivatives, pesticides/herbicides, chromium, radiation and magnetic fields were associated with higher odds of diffuse-type, but not intestinal-type gastric cancer.

**Conclusions:** Based on a large pooled analysis, we identified several occupations and related exposures that are associated with elevated odds of gastric cancer. These findings have potential implications for risk attenuation and could be used to direct investigations evaluating the impact of targeted gastric cancer prevention/early detection programs based on occupation.

### Keywords

gastric neoplasm; epidemiology; environment and public health; digestive system neoplasm

## INTRODUCTION

Gastric cancer is the 5th most common cancer and the 2nd leading cause of cancer-related deaths worldwide.[1] Gastric cancer pathogenesis is multifactorial and represents a complex interaction of host genetic determinants, and microbial virulence factors (primarily, *Helicobacter pylori (H pylori)*), as well as environmental constituents.[2] Research focused on modifiable environmental factors, such as occupational exposures, would inform disease risk attenuation efforts.

There are some data to support the increased risk of gastric cancer with some occupations, including concrete and masonry workers, miners and quarrymen, farmers, fishermen, machine operators, ceramic and textile industry workers, food industry workers, cooks, launderers, and dry cleaners.[3,4] An increased risk has also been described among workers with routine exposures to coal, asbestos dust, organic solvents, pesticides and herbicides, nitrogen oxides, N-nitroso compounds, and ionizing radiation.[5,6] These studies, though, are limited by small sample sizes, inconsistent risk estimates, and variable effort in controlling for relevant confounders. Further, gastric cancer risk estimates according to histologic subtype (intestinal versus diffuse) are even more limited and heterogeneous, with only three prior case-control studies published and with mixed results.[5,7,8]

Thus, there remains a clinically important knowledge gap with respect to the associations between occupational exposures and gastric cancer. To address this gap we performed a pooled analysis of individual-level data from case-control studies participating in the Stomach cancer Pooling (StoP) Project[9], a globally collaborative consortium specifically established to define risk promoting and risk attenuating factors for gastric cancer.

## METHODS

### Study Population

At the time this analysis was conducted, the complete StoP dataset included 31 harmonized case-control and cohort (through a nested case-control approach) studies from across the world, representing a total of 14,465 gastric cancer cases and 34,972 controls. For this study specifically, we included data from 11 studies within the consortium that collected data on occupations and occupational exposures (data collection interval: 1985–2010); these included two studies from Italy (labeled Italy 1 and Italy 2)[10,11], one from Canada[12], one from Russia[13], one from China[14], one from the USA[15], two from Japan (labeled Japan 1[16] and Japan 2[17]), one from Spain[7], and two from Brazil (labeled Brazil 1[18] and Brazil 2[19]). Altogether, these studies included a total of 5279 cases with gastric cancer and 12,297 controls without gastric cancer. Table 1 summarizes the data available from each included study. Additional details of the studies in the StoP consortium and the harmonization process have been previously described in depth.[9]

### Study Definitions

Gastric cancer cases were all histologically confirmed at the time of diagnosis at the respective study sites. Controls were population- (53.8%) or hospital-based (46.2%) individuals without cancer; 54% of controls were age- and sex-matched to cases. Hospital-

based controls were cancer-free individuals admitted to the hospital in the same time period as cases[7,10,13,15–19], while population-based controls were cancer-free individuals randomly selected by geographic location[11,14] or random-digit dialing.[12] Details regarding definitions and categorization of covariates used in this analysis are provided in the supplemental material.

### Primary Outcome

The primary outcome was gastric cancer, histologically classified as intestinal, diffuse-, or mixed-type where available (i.e., in 9 of 11 included studies).

### Harmonization of Occupational and Chemical and Environmental Occupational Exposure Data (Primary Exposure)

All non-occupational data were harmonized centrally at the StoP Pooling Center in Milan, Italy. These data are routinely checked for completeness and consistency between variables. Harmonization of all occupational data was performed specifically for the present analysis. A brief description is provided here, with more detailed information provided in the supplemental material. All occupations and occupational exposures of at least 1-year duration were considered. Because of country-based differences, we coded all occupations according to the International Standard Classification of Occupations 68 (ISCO-68)[19,20], which is a standardized occupational classification system that can be universally applied across countries and time. This was done in a blinded fashion, without knowledge of case versus control status. One-digit ISCO-68 codes were used for harmonizing the more general occupational histories, while the more specific 2-digit ISCO-68 codes were used for detailed occupational history. Importantly, occupations with 2-digit ISCO-68 codes can be collapsed into 1-digit ISCO-68 codes and combined with the general job data to maximize statistical power.

Five studies (Italy 1[10], Canada[12], China[14], USA[15], and Spain[7]) additionally provided occupational chemical and environmental exposure data. To limit heterogeneity, only those environmental/chemical exposures which could be harmonized across at least three studies were included for this analysis. We selected *a priori* those exposures identified by the World Health Organization International Agency for Research on Cancer (IARC) to be carcinogenic to humans (Group 1), probably carcinogenic to humans (Group 2A), or possibly carcinogenic to humans (Group 2B), as listed in the publicly available IARC Monograph, Volumes 1–124.[21] Group 3 agents, which are not classifiable as to their carcinogenicity in humans due to insufficient human data, were not included. Categorization was then performed according to the Canadian Job Exposure Matrix (CANJEM)[20], which is a validated job exposure matrix that provides information on the probability, frequency and intensity of exposures from a list of 258 occupational risk factors. Importantly, CANJEM categories can be cross-referenced with ISCO-68 job codes, which we performed to ensure internal validity of the harmonization process. Accordingly, the selected exposures included Pesticides/Herbicides, Chromium, Asbestos, Radiation and Magnetic Fields, Wood Dust and Lumber Industry, Aromatic Amines, Plastic Dust, Aromatic Hydrocarbons, Volatile Sulfur Compounds, and Coal Derivatives.

## Statistical Analysis

Categorical and continuous variables were compared using the $\chi^2$ statistic and Student *t* test, respectively. Multivariable logistic regression was used to estimate the odds ratio(OR) and corresponding 95% confidence intervals (CI) of gastric cancer. Only occupational codes that included at least 10 subjects were used for effect estimates; thus, 50 out of a maximum 70 2-digit occupational ISCO-68 codes were analyzed. The reference group was defined *a priori* as subjects who had never held the specific occupation or held that occupation for less than one year. Similarly, chemical and environmental exposures were classified as "ever" versus "never" exposure, with the latter considered the reference group—that is, "never" exposure was defined as subjects who had never been exposed to those substances or who were exposed for less than one year; as detailed above, these were categorized using the CANJEM. Of note, unemployed individuals were not included in the analysis due to possibility for selection bias. Stratified analyses according to histologic subtype were performed.

All multivariable logistic regression models were adjusted for geographic location (study ID). Models were also adjusted for potential confounders selected *a priori* based on clinical knowledge of gastric cancer risk factors, including age, gender, education[22], fruit and vegetable consumption[23], alcohol consumption[24], smoking status[25], history of gastric cancer in the first-degree relative, and *H pylori* exposure—as available based on the included studies (Table 1)—as well as variables with $p<0.10$ on the univariable analysis. Covariate categorization (supplemental material) and reference values were already harmonized centrally at the StoP Pooling Center, as previously done in other publications.[9,22–25] No new *H pylori* testing was performed for the purposes of this analysis and all *H pylori* testing was conducted at the individual study sites at the time of the respective study initiation. Eight of the 11 studies (73%) reported *H pylori* exposure status (Table 1), with the majority (7 of 8, 88%) making this determination based on *H pylori* serologic testing by enzyme-linked immunosorbent assay (ELISA); De Feo *et al.* was the only study that reported *H pylori* positivity based on presence of *H pylori* on histopathology. Among tested individuals, positive *H pylori* exposure was defined as positive *H pylori* serology (or histopathology), while negative *H pylori* exposure was defined as negative testing. We acknowledge that these tests have different implications – that is, identification of *H pylori* on histopathology confirms current, active infection while a positive *H pylori* serology confirms a history of infection and cannot discriminate active versus former infection. Because *either* current or former *H pylori* infection is relevant when considering risk of gastric cancer, we included both in the definition of *H pylori* exposure, which also allowed maximal statistical power for our analysis. Notably, considering only active *H pylori* infection would increase the risk of bias since active *H pylori* infection is often lost once gastric preneoplastic changes develop, whereas the *H pylori* seropositivity is maintained.

For covariates with missing or unknown values <10%, individuals with missing values were excluded from the analysis, since these covariates appear to be missing at random with respect to both the exposure and the outcome. The only covariate which exceeded this threshold was *H pylori* status. We performed a sensitivity analysis comparing the odds of gastric cancer according to occupational exposures, either with or without *H pylori* exposure

status in the model, as well as a stratified analysis according to *H pylori* exposure status. All statistical analyses were carried out in SAS 9.4 University Edition (SAS Institute Inc., Cary, NC, USA).

### Ethics and Study Oversight

All participating studies previously received ethical approval from their local Institutional Review Boards (IRBs). For the collaborative re-analysis, *ad hoc* approval was obtained from the University of Milan IRB.

## RESULTS

### Demographics

A total of 5279 gastric cancer cases and 12,297 controls were analyzed. Demographic and study site details are provided in Table 2. With respect to geographic distribution, 26.7% (n=4694) of cases and controls were from Europe, 32.2% (n=5664) from East Asia, and 41.1% (n=7216) from North or South America. There was a similar proportion of population- and hospital-based case-control studies. Generally speaking, cases were more often male and slightly older (median ages 64 vs. 61 years) compared to controls. Additionally, compared to controls, cases more frequently (all $p<0.01$) had lower education, were more frequently current cigarette smokers, more frequently consumed 12g or more alcoholic drinks/day, more frequently had a family history of gastric cancer in a first-degree relative, and more frequently had *H pylori* exposure (43.5% vs 25.8%).

### Odds of gastric cancer according ISCO-68 categorization, stratified by histologic subtype

The adjusted odds of gastric cancer overall for 1-digit broad and 2-digit detailed ISCO-68 occupational codes are provided in Table 3 and Supplemental Table 1, respectively. Occupations are reported below from broad to more detailed occupational categorization.

### 1-digit ISCO-68 codes

The analysis using the broader 1-digit ISCO-68 job categories included more general occupational histories and thus comprised a larger set of study subjects (Table 3). There was a significantly higher adjusted odds ratio of gastric cancer overall in Sales Workers (OR 1.22, 95% CI: 1.07–1.39), Production and Related Workers, Transport Equipment Operators and Laborers (OR 1.18, 95% CI: 1.06–1.31), and Agricultural, Animal Husbandry and Forestry Workers, Fishermen and Hunters (OR 1.17, 95% CI: 1.01–1.35); whereas there was a lower adjusted odds ratio among Administrative and Managerial Workers (OR 0.78, 95% CI: 0.67–0.91) and Clerical and Related Workers (OR 0.74, 95% CI: 0.64–0.85).

When separated according to histologic subtype, there remained a higher adjusted odds ratio for both intestinal- and diffuse-type gastric cancer among Production and Related Workers, Transport Equipment Operators and Laborers, which was of similar magnitude, and a suggestive trend for mixed-type (OR 1.22, 95% CI: 0.99–1.44). By comparison, among Agricultural, Animal Husbandry and Forestry Workers, Fishermen and Hunters, there remained a higher odds ratio of intestinal- (OR 1.29, 95% CI: 1.06–1.57), but not diffuse- or mixed-type gastric cancer. Sales Workers had a higher adjusted odds ratio of diffuse-

(OR 1.39, 95% CI: 1.18–1.65), but not intestinal- or mixed-type gastric cancer. The lower adjusted odds ratio of gastric cancer was unchanged among Clerical and Related Workers, irrespective of histologic subtype. By comparison, the Administrative and Managerial Workers occupational category was associated with a lower odds ratio of intestinal- (OR 0.49, 95% CI: 0.34–0.70) and mixed- (OR 0.68, 95% CI: 0.48–0.98), but not diffuse-type (OR 0.93, 95% CI: 0.77–1.11) gastric cancer, which was notably despite smaller within strata cases for the intestinal- and mixed-types (n=37 and 39).

### 2-digit ISCO-68 codes

Despite smaller per strata numbers for the more detailed 2-digit ISCO-68 codes, there were several occupations which were significantly associated with gastric cancer overall, and according to histologic subtype. (Supplemental Table 1) Occupations with a higher adjusted odds ratio for gastric cancer included Agricultural and Animal Husbandry Workers (OR 1.33, 95% CI: 1.06–1.68), Miners, Quarrymen, Well Drillers and Related Workers (OR 1.70, 95% CI: 1.01–2.88), Blacksmiths, Toolmakers and Machine-Tool Operators (OR 1.41, 95% C:I 1.05–1.89), Bricklayers, Carpenters and Other Construction Workers (OR 1.30, 95% CI: 1.06–1.60), and Stationary Engine and Related Equipment Operators (OR 6.53, 95% CI: 1.41–30.19). Occupations with a lower adjusted odds ratio included Legislative Officials and Government Administrators (OR 0.49, 95% CI: 0.28–0.85), Tailors, Dressmakers, Sewers, Upholsterers, and Related Workers (OR 0.60, 95% CI: 0.42–0.87), Transport Equipment Operators (OR 0.66, 95% CI: 0.55–0.80), and Clerical and Related Workers (OR 0.67, 95% CI: 0.52–0.86). All other associations were null, but there was insufficient power for several strata as noted.

Separation by histologic subtype further reduced per strata numbers but nevertheless unmasked relevant associations. There was a higher adjusted odds ratio of intestinal-type gastric cancer among Agricultural and Animal Husbandry Workers; Blacksmiths, Toolmakers and Machine-Tool Operators; Bricklayers, Carpenters and Other Construction Workers; Building Caretakers, Charworkers, Cleaners and Related Workers; Miners, Quarrymen, Well-Drillers and Related Workers; and Stationary Engine and Related Equipment Operators. There was a significantly higher adjusted odds ratio of diffuse-type gastric cancer among Fishermen, Hunters and Related Workers and Wood Preparation Workers and Paper Makers. There was a lower adjusted odds ratio for the intestinal-type among Legislative Officials and Government Administrators; Clerical and Related Workers; Electrical Fitters and Related Electrical Workers; Material-Handling and Equipment Operators, Dockers, Freight Handlers; and Transport Equipment Operators. There were several occupations with suggestive trends, but these were limited by low per strata numbers for these more detailed categorizations.

### Odds of gastric cancer according to selected chemical and environmental occupational exposures, overall and by histological type (Table 4)

The following occupational exposures were associated with a 30–56% higher odds of gastric cancer overall: Pesticides and Herbicides, Chromium, Asbestos, Radiation and Magnetic Fields, Wood Dust, Aromatic Amines, Plastic Dust, Aromatic Hydrocarbons, Volatile Sulfur Compounds, and Coal Derivatives.

Exposure to Wood Dust (OR 1.51, 95% CI: 1.01–2.26) or Aromatic Amines (OR 1.83, 95% CI 1.09–3.06) was associated with a higher adjusted odds ratio of intestinal-type gastric cancer, while exposure to Asbestos demonstrated a suggestive trend (OR 1.31, 95% CI: 0.96–1.80). Exposure to Coal Derivatives (OR 2.69, 95% CI: 1.29–5.59), Pesticides and Herbicides (OR 1.66, 95% CI: 1.08–2.55), Chromium (OR 1.84, 95% CI: 1.09–3.11), Radiation and Magnetic Fields (OR 2.01, 95% CI: 1.33–3.06), Wood Dust (OR 2.52, 95% CI: 1.46–4.33), and Aromatic Amines (OR 2.92, 95% CI: 1.36–6.26) were all associated with a higher adjusted odds ratio of diffuse-type gastric cancer.

### Odds of gastric cancer stratified by H pylori exposure

The adjusted odds of gastric cancer overall associated with occupations and stratified by *H pylori* exposure status are provided in Supplemental Table 2. Among *H pylori* non-exposed individuals, Production and Related Workers, Transport Equipment Operators and Laborers, was the only occupation category associated with a higher adjusted odds ratio of gastric cancer overall (OR 1.53, 95% CI: 1.10–2.13).

## DISCUSSION

In this comprehensive pooled analysis of individual-level data of 5279 gastric cancer cases and 12,297 controls from the global StoP Consortium, we identified several occupations and occupational exposures that were associated with gastric cancer after at least one year of exposure. In general, there were overall lower odds of gastric cancer among professional, administrative, legislative/executive and clerical workers (i.e. “desk jobs”) but higher odds among labor-related occupations with dust and high-temperature exposures, even after adjusting for relevant confounders. Moreover, several specific occupational exposures were associated with higher odds of gastric cancer after at least one year of exposure, with wood dust and aromatic amine exposure associated with respective 1.5- and 1.8-fold higher odds of intestinal-type gastric cancer, and respective 2.5- and 2.9-fold higher odds of diffuse-type gastric cancer. Exposure to coal derivatives, pesticides/herbicides, chromium, radiation and magnetic fields was also associated with higher odds of diffuse-type cancer, on the order of 1.5- to 2.0-fold higher. These data might have important implications for individual risk stratification, consideration of selected screening or surveillance, and counseling regarding risk factor modification to attenuate gastric cancer risk in susceptible individuals, and should serve as a basis for future investigations.

The mechanisms underlying the association of certain occupations and occupational exposures with gastric cancer are not well-defined, but a few hypotheses have been proposed. The highest risk groups appear to be those in “dusty industries” (e.g. foundry workers, wood workers, grain farmers, coal miners, textile machine operators), as well as occupations with “high temperature” exposures (e.g. metal smelting/refining furnacemen, blacksmiths, railway engine drivers, boilermen, firemen).[4,26,27] Regarding the “dust hypothesis”, mineral and organic dusts are inhaled, trapped in the airway mucus layer, cleared by the cilia and either expectorated or swallowed. If swallowed, there is direct contact with the gastric mucosa by these abrasive and potentially carcinogenic compounds, such as N-nitrosamines, which are common in rubber, metal, agriculture, and leather

industries.[4,27] There were higher odds of gastric cancer in all dust-type exposures. Rubber, nitrates/nitrites, asbestos, and lead compounds are all identified by IARC as gastric carcinogens or probable gastric carcinogens in humans, and lend biological plausibility to several of the associations we identified. Additionally, our finding that occupations with exposure to “Radiation and Magnetic Fields” based on the CANJEM matrix categorization were associated with higher odds of gastric cancer, with a 2-fold significantly higher odds ratio of the diffuse-type, is congruent with the IARC classification of X- and gamma-radiation as Group I gastric carcinogens.[21] Importantly, direct contact of these compounds with the gastric epithelial lining, absorption, or damage due to radiation, acts in concert with host genetic, dietary, microbial and environmental factors to promote carcinogenesis.[2]

Geographic variations also complicate reliable determination of the attributable risk of occupations and occupational exposures on gastric cancer, and is evidenced by the conflicting literature with certain exposures being associated with gastric cancer in some geographies, but not others.[4,27,28] Heterogeneity in the literature might also reflect the different pathogenesis between intestinal- and diffuse-type gastric adenocarcinoma[2,29], since the majority of studies do not discriminate between the two histologic subtypes. Other distinctions between these two subtypes include epidemiological, demographic, and overall prognosis.[30] We identified notable differences in odds of gastric cancer according to histologic subtype, with diffuse-type associated with several more specific exposures versus intestinal-type. This underscores the clinical importance of evaluating histologic subtype in studies going forward, particularly since the risk factors for and the pathogenesis of diffuse-type gastric cancer is less defined versus the intestinal-type.

The literature on occupational exposures and risk of gastric cancer (most often represented as gastric cancer mortality) extends back several decades but with mixed results.[26,27,31–42] Unlike the present study, early studies on occupational exposures rarely accounted for potential confounders including smoking, socioeconomic status, education, diet, and other factors, as less was known about their respective association with gastric cancer at the time. By also adjusting for study geography, we limited potential unmeasured confounders related to regional or cultural variations, which is relevant given the geographic variation in gastric cancer incidence. Individual-level data from the StoP consortium are well-maintained, comprehensive, and undergo regular quality checks.[9] Our study has several additional key strengths, including a high availability of lifetime occupational exposure history and minimal missing data, other than *H pylori* exposure status. We chose *a priori* to include occupations and exposures of at least 1-year duration and prior to gastric cancer diagnosis in order to not only limit the likelihood of identifying prevalent gastric cancers but also to theoretically ensure there is a long enough duration of exposure for the outcome to occur. Other strengths include our categorization of occupations and exposures using validated methods (ISCO-68 and CANJEM) and the global breadth of studies included. Furthermore, using the CANJEM matrix, we cross-referenced the chemical and environmental exposures in our analysis to the occupations that have routine exposure to these agents. For example, based on CANJEM, wood preparation and paper making jobs have a high probability of intense and frequent exposure to wood dust and, in the present analysis, wood dust exposure was associated with 1.5- and 2.5-fold higher odds of intestinal-type and diffuse-type gastric cancer, respectively. We also found correlations between pesticide/herbicide exposure and

farm managers and agriculture and animal husbandry workers; coal derivative exposure and stationary engine operators; and plastic dust exposure and rubber product makers. Collectively, these data support the validity of our methodologic approach, including our standardization and subsequent harmonization of occupations/occupational exposures. It is important to note though that not all occupations, especially the low-risk occupations identified (e.g. administrative, legislative, and clerical workers), have discrete occupation-specific exposures. Shared experiences/environmental exposures related to unmeasured confounders (or incompletely adjusted measured confounders) might also underlie the inverse association between some occupations and gastric cancer. The present study was not designed to identify etiologies for these associations; indeed, future investigations designed with the specific objective of defining risk or protective determinants for gastric cancer among these occupations are warranted.

Because gastric cancer is a rare diagnosis, the case-control design is the optimal design for analyzing exposures associated with the disease. One limitation, which is inherent to case-control studies in general, is recall bias—more specifically recall for covariates such as diet and voluntary adverse lifestyle behaviors (e.g. smoking). That said, since occupation is a concrete exposure, recall bias might be less of an issue. Another consideration is that subjects could have been exposed to more than one occupation over time, the interactions of which have an unpredictable effect on overall disease risk. This is not unique to our analysis and typifies the difficulty in studying the association between intermittent environmental exposures and disease risk. The possibility of selection bias is another consideration, particularly since there was a large proportion, relatively speaking, of hospital-based controls; that said, similar representation of hospital-based and population-based controls might reduce the “healthy worker” effect that is a common source of bias in studies of occupational exposures and which can have an unpredictable effect on the risk estimates.[43] We excluded unemployed individuals from the analysis *a priori*, since their inclusion might contribute to selection bias. Although we did not have complete data on *H pylori* exposure for all studies, our conclusions regarding occupation and the odds of gastric cancer were not changed when restricting the analysis to only studies that provided *H pylori* exposure data. Additionally, because the likelihood of *H pylori* exposure is not plausibly linked *directly* to any of the occupational-types or occupation-related exposures analyzed, we would not expect *H pylori* exposure status to confound our findings. However, we acknowledge that *H pylori* exposure has been associated with lower socioeconomic status, overcrowding and urban versus rural dwelling, poor water sanitation, among other factors which might well be associated with certain occupations.[44] Unmeasured confounders are a limitation of any observational study and we are unable to comment on how socioeconomic status, health insurance/healthcare infrastructure, cultural factors, or other potential shared exposures or experiences related to unmeasured confounders might affect our findings, since these data were not collected. The incidence of gastric cancer varies among the countries included in this analysis; while we adjusted for study location, our findings might not be generalizable to all populations.

In conclusion, we performed a comprehensive pooled analysis of case-control studies in the global StoP consortium and, using validated methods for occupational categorization, we identified several occupations and occupational exposures that are associated with gastric

cancer. We additionally found some notable differences according to intestinal- versus diffuse-type gastric cancer, which supports etiopathogenic differences in these histologic subtypes. Our data can be leveraged to guide future investigations aimed at defining mechanisms of gastric carcinogenesis associated with these exposures. While our findings should be confirmed in other large, well-designed studies with appropriate adjustment for confounders, this should not delay health counseling for these high-risk groups and heightened efforts to motivate risk factor reduction. Whether active interventions such as targeted gastric cancer screening and surveillance efforts are additionally warranted for these high-risk groups remains to be determined.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## Abbreviations:

| | |
|---|---|
| **CANJEM** | Canadian Job Exposure Matrix |
| **CI** | confidence interval |
| **H pylori** | Helicobacter pylori |
| **IRB** | Institutional Review Board |
| **ISCO** | International Standard Classification of Occupations |
| **OR** | odds ratio |
| **StoP** | Stomach cancer Pooling Project |

## References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018; 68: 394–424. [PubMed: 30207593]
2. Polk DB, Peek RM. Helicobacter pylori: gastric cancer and beyond. Nat Rev Cancer 2010; 10: 403–14. [PubMed: 20495574]
3. Chow WH, McLaughlin JK, Malker HS, et al. Occupation and stomach cancer in a cohort of Swedish men. Am J Ind Med 1994; 26: 511–20. [PubMed: 7810549]
4. Raj A, Mayberry JF, Podas T. Occupation and gastric cancer. Postgrad Med J 2003; 79: 252–8. [PubMed: 12782770]

5. Ekström AM, Eriksson M, Hansson LE, et al. Occupational exposures and risk of gastric cancer in a population-based case-control study. Cancer Res 1999; 59: 5932–7. [PubMed: 10606238]
6. Cocco P, Ward MH, Buiatti E. Occupational risk factors for gastric cancer: an overview. Epidemiol Rev 1996; 18: 218–34. [PubMed: 9021314]
7. Santibañez M, Alguacil J, de la Hera MG, et al. Occupational exposures and risk of stomach cancer by histological type. Occup Environ Med 2012; 69: 268–75. [PubMed: 22068174]
8. Krstev S, Dosemeci M, Lissowska J, Chow WH, Zatonski W, Ward MH. Occupation and risk of stomach cancer in Poland. Occup Environ Med 2005; 62: 318–24. [PubMed: 15837853]
9. Pelucchi C, Lunet N, Boccia S, et al. The stomach cancer pooling (StoP) project: study design and presentation. Eur J Cancer Prev 2015; 24: 16–23. [PubMed: 24566154]
10. De Feo E, Simone B, Persiani R, et al. A case-control study on the effect of Apolipoprotein E genotypes on gastric cancer risk and progression. BMC Cancer 2012; 12: 494. [PubMed: 23098561]
11. Buiatti E, Palli D, Decarli A, et al. A case-control study of gastric cancer and diet in Italy. Int J Cancer 1989; 44: 611–6. [PubMed: 2793233]
12. Mao Y, Hu J, Semenciw R, White K, Canadian Cancer Registries Epidemiology Research Group. Active and passive smoking and the risk of stomach cancer, by subsite, in Canada. Eur J Cancer Prev 2002; 11: 27–38. [PubMed: 11917206]
13. Zaridze D, Borisova E, Maximovitch D, Chkhikvadze V. Aspirin protects against gastric cancer: results of a case-control study from Moscow, Russia. Int J Cancer 1999; 82: 473–6. [PubMed: 10404057]
14. Mu L-N, Lu Q-Y, Yu S-Z, et al. Green tea drinking and multigenetic index on the risk of stomach cancer in a Chinese population. Int J Cancer 2005; 116: 972–83. [PubMed: 15856451]
15. Zhang ZF, Kurtz RC, Klimstra DS, et al. Helicobacter pylori infection on the risk of stomach cancer and chronic atrophic gastritis. Cancer Detect Prev 1999; 23: 357–67. [PubMed: 10468887]
16. Matsuo K, Oze I, Hosono S, et al. The aldehyde dehydrogenase 2 (ALDH2) Glu504Lys polymorphism interacts with alcohol drinking in the risk of stomach cancer. Carcinogenesis 2013; 34: 1510–5. [PubMed: 23455379]
17. Machida-Montani A, Sasazuki S, Inoue M, et al. Association of Helicobacter pylori infection and environmental factors in non-cardia gastric cancer in Japan. Gastric Cancer 2004; 7: 46–53. [PubMed: 15052440]
18. Nishimoto IN, Hamada GS, Kowalski LP, et al. Risk factors for stomach cancer in Brazil (I): a case-control study among non-Japanese Brazilians in São Paulo. Jpn J Clin Oncol 2002; 32: 277–83. [PubMed: 12411564]
19. Hamada GS, Kowalski LP, Nishimoto IN, et al. Risk factors for stomach cancer in Brazil (II): a case-control study among Japanese Brazilians in São Paulo. Jpn J Clin Oncol 2002; 32: 284–90. [PubMed: 12411565]
20. ISCO - International Standard Classification of Occupations. http://www.ilo.org/public/english/bureau/stat/isco/ (accessed April 7, 2019).
21. Agents Classified by the IARC Monographs, Volumes 1–124 – IARC Monographs on the Identification of Carcinogenic Hazards to Humans. https://monographs.iarc.fr/agents-classified-by-the-iarc/ (accessed Oct 13, 2019).
22. Rota M, Alicandro G, Pelucchi C, et al. Education and gastric cancer risk - An individual participant data meta-analysis in the StoP project consortium. Int J Cancer 2019; published online March 28. DOI:10.1002/ijc.32298.
23. Bertuccio P, Alicandro G, Rota M, et al. Citrus fruit intake and gastric cancer: The stomach cancer pooling (StoP) project consortium. Int J Cancer 2018; 144: 2936–44.
24. Rota M, Pelucchi C, Bertuccio P, et al. Alcohol consumption and gastric cancer risk-A pooled analysis within the StoP project consortium. Int J Cancer 2017; 141: 1950–62. [PubMed: 28718913]
25. Praud D, Rota M, Pelucchi C, et al. Cigarette smoking and gastric cancer in the Stomach Cancer Pooling (StoP) Project. Eur J Cancer Prev 2016; published online Aug 24. DOI:10.1097/CEJ.0000000000000290.

26. Kneller RW, Gao YT, McLaughlin JK, et al. Occupational risk factors for gastric cancer in Shanghai, China. Am J Ind Med 1990; 18: 69–78. [PubMed: 2378371]
27. Parent ME, Siemiatycki J, Fritschi L. Occupational exposures and gastric cancer. Epidemiology 1998; 9: 48–55. [PubMed: 9430268]
28. Ferro A, Peleteiro B, Malvezzi M, et al. Worldwide trends in gastric cancer mortality (1980–2011), with predictions to 2015, and incidence by subtype. Eur J Cancer 2014; 50: 1330–44. [PubMed: 24650579]
29. Correa P, Piazuelo MB, Wilson KT. Pathology of gastric intestinal metaplasia: clinical implications. Am J Gastroenterol 2010; 105: 493–8. [PubMed: 20203636]
30. Hu B, El Hajj N, Sittler S, Lammert N, Barnes R, Meloni-Ehrig A. Gastric cancer: Classification, histology and application of molecular pathology. J Gastrointest Oncol 2012; 3: 251–61. [PubMed: 22943016]
31. Stocks P A study of cancer mortality in farming, quarrying, mining and other occupations in North Wales and Cheshire. Br J Cancer 1961; 15: 701–11. [PubMed: 13917298]
32. Stukonis M, Doll R. Gastric cancer in man and physical activity at work. Int J Cancer 1969; 4: 248–54. [PubMed: 5347286]
33. Cocco P, Palli D, Buiatti E, et al. Occupational exposures as risk factors for gastric cancer in Italy. Cancer Causes Control 1994; 5: 241–8. [PubMed: 8061172]
34. Sorahan T, Faux AM, Cooke MA. Mortality among a cohort of United Kingdom steel foundry workers with special reference to cancers of the stomach and lung, 1946–90. Occup Environ Med 1994; 51: 316–22. [PubMed: 8199681]
35. Burns PB, Swanson GM. Stomach cancer risk among black and white men and women: the role of occupation and cigarette smoking. J Occup Environ Med 1995; 37: 1218–23. [PubMed: 8542342]
36. Gomes-Carneiro MR, Ribeiro-Pinto LF, Paumgartten FJ. [Environmental risk factors for gastric cancer: the toxicologist's standpoint]. Cad Saude Publica 1997; 13 Suppl 1: 27–38. [PubMed: 10886922]
37. Kang SK, Burnett CA, Freund E, Walker J, Lalich N, Sestito J. Gastrointestinal cancer mortality of workers in occupations with high asbestos exposures. Am J Ind Med 1997; 31: 713–8. [PubMed: 9131226]
38. Cocco P, Ward MH, Dosemeci M. Occupational risk factors for cancer of the gastric cardia. Analysis of death certificates from 24 US states. J Occup Environ Med 1998; 40: 855–61. [PubMed: 9800169]
39. González CA, Sanz M, Marcos G, et al. Occupation and gastric cancer in Spain. Scand J Work Environ Health 1991; 17: 240–7. [PubMed: 1925435]
40. Wu-Williams AH, Yu MC, Mack TM. Life-style, workplace, and stomach cancer by subsite in young men of Los Angeles County. Cancer Res 1990; 50: 2569–76. [PubMed: 2328485]
41. Wright WE, Bernstein L, Peters JM, Garabrant DH, Mack TM. Adenocarcinoma of the stomach and exposure to occupational dust. Am J Epidemiol 1988; 128: 64–73. [PubMed: 3381836]
42. Olsen JH, Møller H, Jensen OM. Risks for respiratory and gastric cancer in wood-working occupations in Denmark. J Cancer Res Clin Oncol 1988; 114: 420–4. [PubMed: 3410880]
43. Shah D Healthy worker effect phenomenon. Indian J Occup Environ Med 2009; 13: 77–9. [PubMed: 20386623]
44. Gupta S, Tao L, Murphy JD, et al. Race/Ethnicity-, Socioeconomic Status-, and Anatomic Subsite-Specific Risks for Gastric Cancer. Gastroenterology 2019; 156: 59–62.e4. [PubMed: 30267713]

## Key Messages

- The associations between occupation type and occupation-specific exposures is incompletely investigated. Further defining such associations has potential public health implications related to gastric cancer.
- Based on a pooled analysis of individual-level data from harmonized case-control studies from centers participating in the Stomach cancer Pooling (StoP) Project, we found that several occupation types were associated with a higher or lower odds ratio of gastric cancer, either overall or according to histologic subtype, after adjusting for relevant confounders.
- We also identified occupation-specific chemical and environmental exposures that were associated with a higher odds ratio of gastric cancer, particularly when analyzed according to histologic subtype (e.g. wood dust, aromatic amines, pesticides and herbicides, coal derivatives, chromium, and others).
- These findings hold clinical importance for better understanding factors positively or inversely associated with gastric cancer, particularly those which are modifiable.
- These findings, if confirmed, might also be used to identify individuals at higher risk of gastric cancer who might benefit from gastric cancer screening and surveillance.

**Table 1:**

Summary of study characteristics and data elements for the studies included from the Stomach cancer Pooling Project (StoP) consortium

| Study ID (Reference) | CASES | CONTROLS | EDUCATION | SOCIO-DEMOGRAPHIC | SMOKING HISTORY | ALCOHOL CONSUMPTION | DIET | FAMILY HISTORY OF GASTRIC CANCER | *HELICOBACTER PYLORI* EXPOSURE* | DETAILED OCCUPATIONAL HISTORY | GENERAL OCCUPATIONAL HISTORY | OCCUPATIONAL CHEMICAL EXPOSURE |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **ITALY 1** (DeFeo *et al.*, 2012) | 164 | 444 | X | X | X | X | X | X | X | | X | X |
| **ITALY 2** (Buiatti *et al.*, 1989) | 1016 | 1159 | X | X | X | X | X | X | | X | | |
| **CANADA** (Mao *et al.*, 2002) | 1132 | 5039 | X | X | X | X | X | | | | | X |
| **CHINA** (Mu *et al.*, 2005) | 206 | 415 | X | X | X | X | X | X | X | | X | X |
| **RUSSIA** (Zaridze *et al.*, 1999) | 448 | 610 | X | X | X | X | X | X | X | X | | |
| **USA** (Zhang *et al.*, 1999) | 114 | 132 | | X | X | X | X | X | | | | X |
| **JAPAN 1** (Matsuo *et al.*, 2013) | 1250 | 3911 | | | X | X | X | X | X | | X | |
| **SPAIN** (Santibanez *et al.*, 2012) | 444 | 455 | X | X | X | X | X | X | X | X | | X |
| **BRAZIL 1** (Nishimoto *et al.*, 2002) | 236 | 236 | X | X | X | X | X | X | X | X | | |
| **BRAZIL 2** (Hamada *et al.*, 2002) | 96 | 192 | X | X | X | X | X | X | X | X | | |
| **JAPAN 2** (Machida-Montani *et al.*, 2004) | 153 | 301 | | | X | X | X | X | X | | X | |

Note: “X” denotes that these data were collected and available for that study

* These studies included data on *H pylori* exposure status, which was determined based on serologic testing (7 studies) or histpopathology (1 study, De Feo et al). A positive exposure was defined as either positive serology or histopathology (see text for additional details)

**Table 2.**

Demographic characteristics of cases and controls from the studies included

| | CASES, N (%) | CONTROLS, N (%) |
|---|---|---|
| **Variables, Study ID (reference)** | N=5279 | N=12297 |
| **Europe** | | |
| **ITALY 1 (**DeFeo *et al.*, 2012) | 160 (3.0) | 444 (3.6) |
| Italy 2 (Buiatti *et al.*, 1989) | 1016 (19.3) | 1159 (9.4) |
| Russia (Zaridze *et al.*, 1999) | 450 (8.5) | 611 (5.0) |
| Spain (Santibanez *et al.*, 2012) | 401 (7.6) | 455 (3.7) |
| **Asia** | | |
| China (Mu *et al.*, 2005) | 206 (3.9) | 415 (3.4) |
| Japan 1 (Matsuo *et al.*, 2013) | 1260 (23.9) | 3327 (27.1) |
| **JAPAN 2 (**Machida-Montani *et al.*, 2004) | 153 (2.9) | 303 (2.5) |
| **North America** | | |
| Canada (Mao *et al.*, 2002) | 1182 (22.4) | 5039 (40.1) |
| USA (Zhang *et al.*, 1999) | 132 (2.5) | 132 (1.1) |
| **South America** | | |
| Brazil 1 (Nishimoto *et al.*, 2002) | 226 (4.3) | 226 (1.8) |
| Brazil 2 (Hamada *et al.*, 2002) | 93 (1.8) | 186 (1.5) |
| **Study type** | | |
| Population-based case-control | 2404 (45.5) | 6613 (53.8) |
| Hospital-based case-control | 2875 (54.5) | 5684 (46.2) |
| **Sex** | | |
| Male | 3492 (66.2) | 7219 (58.7) |
| Female | 1787 (33.8) | 5078 (41.3) |
| **Age at diagnosis or interview, years**, Median (interquartile range, IQR) | 64 (55–74) | 61 (50–68) |
| **Education** [1] | | |
| None | 649 (17.4) | 657 (7.7) |
| Primary school | 1203 (32.2) | 1413 (16.6) |
| Middle school | 639 (17.1) | 1451 (17.0) |
| High school | 850 (22.8) | 3666 (43.0) |

| | CASES, N (%) | CONTROLS, N (%) |
|---|---|---|
| ≥ College graduate | 239 (6.4) | 843 (9.8) |
| Missing | 154 (4.1) | 505 (5.9) |
| **History of gastric cancer in first-degree relatives** [2] | | |
| Yes | 482 (11.8) | 446 (6.2) |
| No | 3353 (81.8) | 6194 (85.3) |
| Missing | 262 (6.4) | 618 (8.5) |
| **Vegetable and fruit intake (study-specific tertiles)** | | |
| Low | 1570 (29.7) | 3816 (31.0) |
| Intermediate | 1635 (31.0) | 3836 (31.2) |
| High | 2057 (39.0) | 4577 (37.2) |
| Missing | 17 (0.3) | 68 (0.6) |
| **Alcohol intake (g/day)** | | |
| Never | 1610 (30.5) | 3901 (31.7) |
| Low (≤ 12) | 1078 (20.4) | 3645 (29.7) |
| Intermediate (> 12 and ≤ 47) | 1640 (31.1) | 2962 (24.1) |
| High (> 47) | 678 (12.8) | 1034 (8.4) |
| Missing | 273 (5.2) | 755 (6.1) |
| **Smoking status (cigarette equivalents/day)** | | |
| Never | 1970 (37.3) | 5308 (43.2) |
| Former | 1663 (31.5) | 3858 (31.4) |
| Current low (≤ 10) | 251 (4.8) | 692 (5.6) |
| Current intermediate (10–20) | 645 (12.2) | 1292 (10.5) |
| Current high (> 20) | 491 (9.3) | 854 (6.9) |
| Missing | 259 (4.9) | 293 (2.4) |
| ***Helicobacter pylori* exposure** [3] | | |
| Positive | 1283 (43.5) | 1543 (25.8) |
| Negative | 610 (20.7) | 1347 (22.6) |
| Missing | 1056 (35.8) | 3077 (51.6) |

[1] No information available for studies USA (Zhang et al., 1999), Japan 1 (Matsuo et al., 2013), and Japan 2 (Machida-Montani et al., 2004).

[2] No information available for Canada (Mao et al., 2002).

[3] *H pylori* exposure data were not reported in the following three studies: Italy 2 (Buiatti et al., 1989), Canada (Mao et al., 2002), and USA (Zhang et al., 1999). For the remaining 8 studies that included *H pylori* data, a positive exposure was defined as either positive serology (7 of 8 studies) or histopathology (1 study, De Feo et al.).

**Table 3.**

Odds of gastric cancer[1,2] overall and according to histologic subtype based on broad occupational categorization (1-digit ISCO 68)

| 1-digit ISCO 68 Code[3] | Job Title | Non-cancer controls (n=5573) | Gastric adenocarcinoma, any histologic subtype (n=3416) | | | Intestinal-type adenocarcinoma (n=1245) | | | Diffuse-type adenocarcinoma (n=1323) | | | Mixed/Unclassified adenocarcinoma (n=677) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | cases | aOR | (95% CI) | cases | aOR | (95% CI) | cases | aOR | (95% CI) | cases | aOR | (95% CI) |
| **1** | Professional, Technical and Related Workers | 500 | 205 | 0.89 | (0.74–1.07) | 68 | 1.00 | (0.74–1.34) | 87 | 0.97 | (0.75–1.24) | 40 | 0.72 | (0.51–1.03) |
| **2** | Administrative and Managerial Workers | 783 | 281 | 0.78 | (0.67–0.91) | 37 | 0.49 | (0.34–0.70) | 204 | 0.93 | (0.77–1.11) | 39 | 0.68 | (0.48–0.98) |
| **3** | Clerical and Related Workers | 953 | 338 | 0.74 | (0.64–0.85) | 75 | 0.70 | (0.54–0.92) | 143 | 0.72 | (0.59–0.87) | 49 | 0.70 | (0.51–0.96) |
| **4** | Sales Workers | 765 | 447 | 1.22 | (1.07–1.39) | 98 | 0.93 | (0.73–1.18) | 248 | 1.39 | (1.18–1.65) | 75 | 1.12 | (0.85–1.46) |
| **5** | Service Workers | 348 | 313 | 0.98 | (0.82–1.18) | 170 | 1.03 | (0.82–1.28) | 74 | 0.88 | (0.65–1.18) | 65 | 1.14 | (0.83–1.57) |
| **6** | Agricultural, Animal Husbandry and Forestry Workers, Fishermen and Hunters | 589 | 545 | 1.17 | (1.01–1.35) | 274 | 1.29 | (1.06–1.57) | 121 | 1.06 | (0.84–1.34) | 110 | 1.07 | (0.81–1.40) |
| **7/8/9** | Production and Related Workers, Transport Equipment Operators and Laborers | 1635 | 1287 | 1.18 | (1.06–1.31) | 523 | 1.17 | (1.01–1.36) | 446 | 1.17 | (1.02–1.35) | 299 | 1.20 | (0.99–1.44) |

[1]Models were adjusted for study location, age, sex, educational achievement, smoking status, alcohol consumption, diet, family history of gastric cancer, and *Helicobacter pylori* exposure. The reference group was defined *a priori* as subjects who had never held the specific occupation or held that occupation for less than one year; unemployed individuals were excluded from the analysis (see text).

All other occupational fields were the reference category

[2]Includes subjects from studies Italy 2 (Buiatti et al., 1989), Russia (Zaridze et al., 1999), USA (Zhang et al., 1999), Spain (Santibanez et al., 2012), Brazil 1 (Nishimoto et al., 2002), Brazil 2 (Hamada et al., 2002), and Japan 2 (Machida-Montani et al., 2004)

[3]ISCO 68, International Standard Classification of Occupations of 1968

**Table 4.**

Odds of gastric cancer[1] overall and according to histologic subtype based on selected chemical or environmental occupational exposures

| | | | Gastric adenocarcinoma (any histologic subtype) | | | Intestinal-type adenocarcinoma | | | Diffuse adenocarcinoma | | | Mixed/Unclassified adenocarcinoma | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Studies[2]** | **Exposure[3]** | **Non-cancer controls (n=10487)** | **Cases** | **OR** | **(95%CI)** | **Cases** | **OR** | **(95% CI)** | **Cases** | **OR** | **(95% CI)** | **Cases** | **OR** | **(95% CI)** |
| 7,10,12,14,15 | Pesticide/Herbicide | 1489 | 650 | 1.42 | (1.25–1.61) | 86 | 1.26 | (0.92–1.73) | 39 | 1.66 | (1.08–2.55) | 374 | 1.46 | (1.25–1.69) |
| 7,10,12,15 | Chromium | 843 | 345 | 1.51 | (1.30–1.76) | 39 | 1.14 | (0.76–1.72) | 23 | 1.84 | (1.09–3.11) | 283 | 1.55 | (1.32–1.82) |
| 7,10,12,15 | Asbestos | 1060 | 438 | 1.35 | (1.17–1.55) | 85 | 1.31 | (0.96–1.80) | 30 | 1.05 | (0.67–1.64) | 319 | 1.43 | (1.22–1.67) |
| 7,10,12,15 | Radiation and Magnetic Fields[4] | 1071 | 426 | 1.30 | (1.13–1.50) | 81 | 1.17 | (0.85–1.60) | 48 | 2.01 | (1.33–3.06) | 287 | 1.26 | (1.07–1.47) |
| 7,10,12,15 | Wood Dust and Lumber Industry | 1520 | 510 | 1.33 | (1.16–1.52) | 46 | 1.51 | (1.01–2.26) | 25 | 2.52 | (1.46–4.33) | 434 | 1.29 | (1.11–1.49) |
| 10,12,15 | Aromatic Amine[5] | 863 | 324 | 1.56 | (1.33–1.82) | 23 | 1.83 | (1.09–3.06) | 12 | 2.92 | (1.36–6.26) | 288 | 1.52 | (1.29–1.79) |
| 7,10,12 | Plastic Dust[6] | 853 | 314 | 1.44 | (1.23–1.68) | 24 | 1.02 | (0.62–1.66) | 12 | 1.50 | (0.76–2.94) | 278 | 1.49 | (1.26–1.75) |
| 7,12,15 | Aromatic Hydrocarbons[7] | 947 | 345 | 1.41 | (1.21–1.64) | 29 | 1.03 | (0.66–1.62) | 12 | 1.08 | (0.56–2.08) | 303 | 1.48 | (1.26–1.74) |
| 7,12,15 | Volatile Sulfur Compounds[8] | 746 | 351 | 1.33 | (1.14–1.55) | 76 | 0.98 | (0.69–1.38) | 29 | 1.14 | (0.70–1.86) | 246 | 1.45 | (1.22–1.72) |
| 7,12,15 | Coal Derivatives[9] | 1095 | 491 | 1.48 | (1.27–1.72) | 71 | 1.29 | (0.76–2.18) | 44 | 2.69 | (1.29–5.59) | 339 | 1.47 | (1.26–1.73) |

[1] Models adjusted for study location, age, sex, education, smoking status, alcohol consumption, diet, GC family history, and *H. pylori* exposure. The reference group was defined *a priori* as subjects without exposure to that particular agent, or exposure for less than one-year (see text).

[2] Includes subjects from studies 10-Italy 1 (De Feo et al., 2012), 12-Canada (Mao et al., 2002), 14-China (Mu et al., 2005), 15-USA (Zhang et al., 1999), and 7-Spain (Santibanez et al., 2012).

[3] Selected exposures were a priori determined based on the International Association for Cancer Research (IARC) Monograph identifying these substances as carcinogenic or potentially carcinogenic (see text)

[4] Defined as exposure to ‘UV rays’, ‘ionizing radiation’, ‘radiation sources’, ‘radiation’, and ‘low-frequency magnetic fields’

[5] Defined as exposure to ‘aromatic amines’, ‘benzidine’, and ‘beta-naphthyl’

[6] Defined as exposure to ‘vinyl chloride’ and ‘synthetic polymer dust’

[7] Defined as exposure to 'benzene' and 'aromatic hydrocarbon solvents'

[8] Defined as exposure to 'mustard gas' and 'volatile sulfur compounds'

[9] Defined as exposure to 'asphalt', 'coal tar', 'soot', 'pitch', 'creosote', and 'bitumen fumes'