

Air pollution and incidence of cancers of the stomach and the upper aerodigestive tract in the European Study of Cohorts for Air Pollution Effects (ESCAPE)

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Running title: Air pollution and gastric and UADT cancers.

Unstructured Abstract: 250 270

Text: 5000 3043

References: 50 29

Abstract:

Air pollution has been classified as carcinogenic to humans. However, to date little is known about the relevance for cancers of the stomach and upper aerodigestive tract (UADT). We investigated the association of long-term exposure to ambient air pollution with incidence of gastric and UADT cancer in 11 European cohorts.

Air pollution exposure was assigned by land-use regression models for particulate matter (PM) below 10 μm (PM_{10}), below 2.5 μm ($\text{PM}_{2.5}$), between 2.5 and 10 μm ($\text{PM}_{\text{coarse}}$), $\text{PM}_{2.5}$ absorbance and nitrogen oxides (NO_2 and NO_x) as well as approximated by traffic indicators. Cox regression models with adjustment for potential confounders were used for cohort-specific analyses. Combined estimates were determined with random effects meta-analyses.

During average follow-up of 14.1 years of 305 551 individuals, 744 incident cases of gastric cancer and 933 of UADT cancer occurred. The hazard ratio for an increase of 5 $\mu\text{g}/\text{m}^3$ of $\text{PM}_{2.5}$ was 1.38 (95%-CI 0.99;1.92) for gastric and 1.05 (95%-CI 0.62;1.77) for UADT cancers.

No associations were found for any of the other exposures considered. Adjustment for additional confounders and restriction to study participants with stable addresses did not influence markedly the effect estimate for $\text{PM}_{2.5}$ and gastric cancer. Higher estimated risks of gastric cancer associated with $\text{PM}_{2.5}$ was found in men (HR 1.98 (1.30;3.01)) as compared to women (HR 0.85 (0.5;1.45)).

This large multicentre cohort study shows an association between long-term exposure to $\text{PM}_{2.5}$ and gastric cancer, but not UADT cancers, suggesting that air pollution may contribute to gastric cancer risk.

Key words: gastric cancer, upper aerodigestive tract cancer, air pollution, epidemiology, ESCAPE

Introduction

Gastric cancer is still one of the most common cancers world-wide with general about 2 fold higher rates in men⁽¹⁾. About 90% of gastric cancers are adenocarcinoma. Due to differences in epidemiologic pattern gastric cancer of the cardia (as connection with the oesophagus) and non-cardia are frequently distinguished⁽²⁾. UADT cancers are closely anatomically located and have overlapping risk factor profiles with those of gastric cancer.

Among the established risk factors of gastric cancer are chronic infection with *Helicobacter (H.) pylori*, smoking, socio-economic status and diet⁽²⁾. Occupational exposure to dusty and high temperature environments was associated with an increased risk of gastric cancer of the diffuse subtype^(3,4). In a prospective Danish Diet Cancer and Health cohort study, no increased risks of oesophageal and gastric cancer were found to be associated with long-term exposure to ambient air pollution with nitrogen oxides (NO_x) and the amount of road or motorized traffic near the baseline residence⁽⁵⁾. An occupational cohort study revealed increased gastric cancer incidence among workers exposed to diesel exhaust⁽⁶⁾. Indirect evidence comes from a study on traffic-related ambient air pollution and gastric cancer mortality in Taiwan that used petrol station density as indicator for exposure to benzene and other hydrocarbons⁽⁷⁾. There is some evidence from a case-control study suggesting that airborne risk factors from occupation such as construction work, bricklayers, lorry and van drivers⁽⁸⁾ and smoking⁽⁹⁾ are associated with elevated risk of cancer in the UADT. Therefore, it is possible that long term outdoor air pollution may have effects on gastric and UADT cancer. Outdoor air pollution has been classified as carcinogenic to humans based on sufficient evidence of carcinogenicity in humans and experimental animal studies as well as strong support by mechanistic studies¹⁰. Most former studies were limited by either proxy variable for air pollution or cancer mortality as end-point. For lung cancer increased risk was consistently observed¹¹. However, for other cancer sites such as stomach and UADT cancers data from large prospective studies with reliable exposure assessment for outdoor air pollution are largely lacking⁽¹²⁾.

Thus, the aim of this study was to examine the association between outdoor air pollution and the risk for cancer of the stomach and UADT using the data and the methodology developed in the European Study of Cohorts for Air Pollution Effects (ESCAPE) project.

Material and Methods

Study population

For the present study, prospective cohort data from 11 geographical areas (Figure 1) that had participated in ESCAPE⁽¹¹⁾ were analysed: Sweden (European Prospective Investigation into Cancer and Nutrition [EPIC]-Umeå; [CEANS] comprising the Swedish National Study on Aging and Care in Kungsholmen [SNAC-K], Stockholm Screening Across the Lifespan Twin study and TwinGene [SALT], Stockholm 60 years old and IMPROVE study [Sixty] and the Stockholm Diabetes Prevention Program [SDPP]), Norway (Oslo Health Study [HUBRO]), Copenhagen, Denmark (Diet, Cancer and Health study [DCH]), the Netherlands (EPIC-Monitoring Project on Risk Factors and Chronic Diseases in the Netherlands [MORGEN], and EPIC-PROSPECT), the United Kingdom (EPIC-Oxford), Austria (Vorarlberg Health Monitoring and Prevention Programme [VHM&PP]), Italy (EPIC-Varese, EPIC-Turin, Italian Studies of Respiratory Disorders in Childhood and Environment [SIDRIA]-Rome) and Spain (EPIC-San Sebastian). To augment the number of cases in the cohort specific analyses, the data of the four cohorts in the Stockholm area and the two cohorts in the Netherlands, respectively, were pooled. For the UADT-analysis the two cohorts from Northern Italy were also pooled. Therefore, 11 cohort estimates contributed to the gastric cancer meta-analysis and 10 to the UADT cancer meta-analysis (Table 1, for cohort-specific details see supplemental Tables S1 and S2).

Urban, peri-urban and rural areas were studied, since data have been collected in large cities and the surrounding as well as in extended geographic areas including rural communities.

The cohort studies and the use of their data in ESCAPE were approved by the local ethical and data protection authorities.

Outcome definition

Follow-up was based on linkage to national or local cancer registries, with exception of SIDRIA Rome

for which hospital discharge and mortality register data were used. The main outcomes were all cancers of the stomach and of the UADT, respectively. Secondary analyses addressed cancer of the cardia, and adenocarcinomas and squamous-cell carcinomas of the UADT. Carcinomas were identified using the International Statistical Classification of Diseases and Related Health Problems, 9th and 10th revision [ICD9 and ICD10]: for gastric cancer C16 [ICD10] and 151 [ICD9], and for UADT cancers: C01-06 and 141-145 (oral cavity), C09, C10 (oropharynx), C12, C13 (hypo-pharynx) and 146 (pharynx), C14, C32 and 161 (larynx), C15 and 150 (esophagus). Lymphomas/myelomas/leukemias were excluded according to the International Classification of Diseases for Oncology (ICDO-3) 9590-9989.

We only included primary cancers and only malignant tumors with ICDO morphology code “3”.

Cancer of the cardia was defined by C16.0 and ICD-9 code 151.0. UADT-cancers were separately analyzed for ICDO-3 morphology codes 8050-8076 (squamous cell carcinoma) and 8140-8141, 8191-8231, 8260-8263, 8310, 8430, 8480-8490, 8560, 8570-8572 (adenocarcinoma). This information was not available for all cohorts.

Exposure assessment

Exposures at the residential baseline address of the participants were determined according to a standardized procedure by assigning air pollution exposure estimates derived from land use regression (LUR) models specifically developed for the respective areas. A detailed description of these models is found elsewhere ^(13,14). In brief, dedicated measurement campaigns (three two week periods) were carried out in each study area over one year between October 2008 and May 2011 to capture the following pollutants: nitrogen dioxide (NO₂) and NO_x; particles with aerodynamic diameters of less than 2.5 µm (PM_{2.5}) and less than 10 µm (PM₁₀) and PM_{2.5} absorbance (determined as the reflectance of PM_{2.5} filters). PM_{coarse} was calculated as PM₁₀ minus PM_{2.5}. PM was measured at 20 locations and NO₂ and NO_x at 40 in each area. In three study areas (Basque country (San Sebastian), Varese, Umeå) only NO₂ and NO_x were measured (Figure 1). Study area-specific LUR models were developed to explain the spatial variation of measured annual average air pollution concentrations within each area using traffic and land-use variables from a Geographic Information System as predictors.

In addition, traffic intensity on the nearest road (vehicles per day) and total traffic load (intensity \times length) on all major roads within a 100-m buffer were used as indicators of traffic exposure. In a sensitivity analysis, we took into account historic developments in air pollution levels by back-extrapolation of pollutant concentrations to the baseline year using data from routine monitoring stations in the study areas. The absolute difference and the ratio between the baseline and 2008-2011 period concentrations were used to calculate back-extrapolated values (for details see⁽¹⁵⁾ and <http://www.escapeproject.eu/manuals/>). Related to availability of historical data from monitoring sites, back-extrapolation for NO₂ was possible for most cohorts while back-extrapolation for PM₁₀ and PM_{2.5} were only possible in 2 and 1 cohorts, respectively.

Statistical analyses

Cohort-specific analyses were carried out using a common protocol and a centrally developed STATA analysis script. This resulted for gastric cancer in eight estimates for PM (11 for NO_x) (see Figure 1) and for UADT cancer in seven estimates for PM (10 for NO_x). For simplicity, these entities are referred to as cohorts in the following results section, tables and figures. When data of multiple cohorts were pooled, the analyses were performed stratifying for cohorts.

Cox proportional hazard -regression with age as the underlying time-axis was carried out with exposure as continuous exposure variable introduced into the model with a linear term. Censoring was applied at the time of death, a diagnosis of any other cancer (except non-melanoma skin cancer) or end of follow-up, whichever came first. Model checks included a test for deviation from proportional hazard assumption and testing the linearity assumption in the relation between each exposure and the log odds of the outcome by replacing the linear term with a natural cubic spline with three equally spaced inner knots. The model fits of the linear and the spline models were compared using a likelihood-ratio test.

Confounder sets were determined *a priori* with increasing complexity. Information on confounder variables in particular smoking status was based on baseline data. Model 1 was adjusted for age (time scale), calendar year and sex. Model 2 was additionally adjusted for smoking status, smoking intensity, smoking duration, occupational exposure, employment status and educational level as indicators for individual socio-economic status (SES). Information on occupational exposure was available for the DCH cohort. For gastric cancer jobs in the following industries were classified as exposure: asbestos, painters, inorganic lead, rubber industry, miners and quarrymen, farmers, fishermen, masonry and concrete workers, machine operators, nurses, food industry workers, cooks, launderers and dry cleaners^{16,17}. For UADT cancers the respective industries were: construction, including reinforced concreters, bricklayers, painters and workers employed in the construction of roads or the erection of roofs⁸. Model 3 (the main model) was in addition adjusted for area-level (residential neighborhood or similar) (SES). The availability of these variables varied slightly between cohorts (supplemental Table S2). Sensitivity analyses including alcohol consumption, environmental tobacco smoke (ETS), intake of fruit, intake of meat and marital status were performed. Only complete case analyses were performed. In the few cases, where one variable was missing entirely, the cohort was nevertheless analyzed using the available confounders (see Table S2). Additional sensitivity analyses were carried out by (i) restricting to participants with stable residence during follow-up or for at least 10 years, (ii) using of back-extrapolated exposure data and (iii) adding an indicator for urban/rural environment to the main model. Information on stable residence was available from either population registries or specific follow-up data from the cohorts.

We first specified single pollutant models. We performed two-pollutant models to test whether associations are independent of other air pollutants. As in other ESCAPE publications, we only included cohorts where the correlation between the two pollutants was lower than 0.7 to avoid multicollinearity (e.g. ⁽¹⁸⁾). Effect modification was assessed for sex, smoking status, educational level and fruit intake. Stratum specific effect estimates were calculated using an interaction term. All cohort-specific analyses were done in STATA versions 10 to 14 (StataCorp, College Station, TX).

The results obtained from the cohort-specific analyses were combined with random effects meta-analysis when estimates for at least three cohorts were available⁽¹⁹⁾. Heterogeneity between cohorts was tested by the χ^2 test from Cochran's Q statistic and quantified with the I²²⁰. STATA version 14 (StataCorp) was used for meta-analyses.

Results

Data on more than 300 000 individuals at risk were included in the analysis. Recruitment of the participants occurred largely in the 1990s. During the mean follow-up of 14.1 years 744 incident cases of gastric cancer and 933 of UADT cancer occurred. DCH and VHM&PP contributed most of the cases (Table 1). Cancer subtypes (i.e. cardia, adenocarcinoma) were in some cohorts too infrequent (<7) to allow analysis. Mean age ranged from 43 years (VHM&PP) to 57 years (DCH). The frequency of current smokers ranged from 11% (EPIC Oxford) to 40% (SIDRIA) (see supplemental Table S1). There was a wide range of air pollution concentrations within and between study areas, with generally the lowest values in the Nordic and the highest levels in the Southern European study areas (Table 1).

The meta-analysis results from the main model showed a positive association of $PM_{2.5}$ with gastric cancer incidence with a hazard ratio (HR) of 1.38 (0.99; 1.92) for an increase of $5\mu g/m^3$ (Table 2, Figure 2). The cohort-specific HR estimates were all higher than one, except for HUBRO (Figure 2). Effect estimates were not much affected by different adjustments (Table 2), notably also not by adjustment for dietary variables including alcohol consumption. None of the other exposure metrics was associated with gastric cancer.

The association of $PM_{2.5}$ with gastric cancer was robust to further adjustment for dietary variables and ETS (Figure 3) as well as for the rural indicator. Restriction to the population with a stable residence resulted in slightly increased effect estimates, however with wider CIs. Because the VHM&PP cohort was the most influential cohort in the $PM_{2.5}$ meta-analysis, we conducted a sensitivity analysis without this cohort. For $PM_{2.5}$ the risk of gastric cancer increased and the confidence intervals became wider (per $5\mu g/m^3$ increase HR 1.68; 0.98-2.88). In the two-pollutant models, the effect estimated for $PM_{2.5}$ remained similar after adjustment with $PM_{2.5}$ absorbance and it increased slightly when adjusting for NO_2 (from 1.32 (0.94; 1.87) to 1.45 (0.97; 2.16) data on six cohorts), PM_{coarse} (from 1.33 (0.94; 1.89) to 1.48 (1.03; 2.15) data on seven cohorts)).

Sensitivity analysis with back-extrapolated values for NO₂ (ratio method) resulted in a slight decrease of the effect estimate of 1.06 of the 10 cohorts with historical data on NO₂ (without HUBRO, Norway) to 1.02 (see supplemental Figure S1). Deviation from linearity of the association at the 5%-level was only observed in four of 102 tests (see supplemental Table S3).

Men showed a higher risk for gastric cancer related to PM_{2.5} with a HR of 1.98 (1.30; 3.01) as opposed to 0.85 (0.5; 1.45) for women (p-value 0.014 for interaction). A similar pattern was seen for the other PM-metrics with HRs above 1.4 for men and approximately 0.50 to 0.6 for women (Figure 4). This pattern seemed to be driven mainly by the participants from Sweden and Rome, and partly Austrian and Dutch cohorts. There was no suggestion of effect modification for fruit consumption, educational level or smoking for any of the exposures (see supplemental Table S4 for smoking).

For cancers of the cardia, the effect estimate for the association with PM_{2.5} was very similar to the estimate for all gastric cancer, and slightly elevated when compared to the same set of cohorts entering the meta-analysis, however confidence intervals were very large (Table 3). In the meta-analyses, 148 cardia cases (six cohorts), 126 adenocarcinomas (six cohorts) and 689 squamous carcinomas (eight cohorts) of the UADT were included, less for PM (Table 3).

For UADT cancer and PM_{2.5}, the HRs for adeno and squamous cell carcinomas were very imprecise and show no clear association. No robust associations were observed for any of the other exposure metrics with any of the cancer subtypes.

Discussion

This analysis of more than 300 000 subjects from diverse geographic areas shows an association between long-term exposure to $PM_{2.5}$ and gastric cancer risk, with a stronger association in men than in women. No further associations between air pollution and cancer risk of the stomach and UADT were found.

We found that an increase of $5.0 \mu g/m^3$ $PM_{2.5}$ increased gastric cancer risk by 38%. Additional adjustment for fruit and vegetable intake did not substantially change these results. Our observation that traffic density and traffic load were not associated with gastric cancer risk is in line with the findings from Raaschou-Nielsen et al. 2011⁽⁵⁾. However, overall $PM_{2.5}$ is less heterogeneously distributed than traffic emissions and is emitted by several sources including e.g. industry, household heating and also subject to long range transport and these other sources may contribute to increased risk of gastric cancer. In line with our findings, Turner et al. observed a significant positive association of near-source $PM_{2.5}$ and stomach cancer mortality in the Cancer Prevention Study II (Turner et al. 2017). In this study gastric cancer mortality is the end point, which reflects both cancer incidence and survival. In a Taiwanese study, areas with high petrol station density were associated with increased gastric cancer mortality⁽⁷⁾. However, the density of petrol station is only a crude proxy for traffic density and outdoor air pollution. A study from Denmark including more than 50 000 persons, which are partially included in the present study, found no association between NO_x and living near a street with high traffic density $> 10\,000$ vehicles per day within 50 m as indicators for traffic-related air pollution and incidence of stomach cancer⁽⁵⁾. Their observation is consistent with our observation that NO_x and NO_2 were not associated with increased risk of gastric cancer.

The association between $PM_{2.5}$ and gastric cancer risk is consistent with findings from airborne occupational exposures and smoking. In the EPIC cohort, current cigarette smoking increased gastric cancer risk by 79 % compared to never smoking⁽²¹⁾. In their study, the association was stronger for gastric cancer cases at the cardia than on the distal part of the stomach (current vs. never smoker HR 4.10 (1.76;9.57) and HR 1.94 (1.05;3.60), respectively)⁽²¹⁾, while we saw no difference for cancer of

the cardia. The consistency of the HRs between the cohorts indicates that the association between PM_{2.5} and gastric cancer is no chance finding. Further support for an association between PM_{2.5} and cancer risk comes from other ESCAPE studies, in which PM_{2.5} together with PM₁₀ was the pollutant that was most clearly and strongly associated with increased risks of lung and kidney cancer ^(11,22).

We found no association between air pollution and cancers of the UADT. UADT is a heterogeneous disease group, with to date little knowledge about risk factors⁽²³⁾. However, airborne risk factors from occupation⁽⁸⁾, indoor air pollution from solid fuel combustion^(24,25) and from smoking⁽⁹⁾ are associated with increased risk of UADT cancers suggesting that air pollution from traffic could also be associated with risk of UADT.

Several mechanisms have been suggested to explain the effect of PM on cancer risk such as oxidative stress induced DNA damage⁽²⁶⁾. Some PM may persist and cause inflammation in the respiratory tract and maybe also in the stomach⁽¹²⁾. Results of an animal study in rats showed, that ultrafine particles were also present in the gastrointestinal tract⁽²⁷⁾ suggesting that other here unmeasured components of PM_{2.5} air pollution may contribute to increased cancer risk.

The findings of our study suggested that compared to women, men may have a higher risk of gastric cancer following exposure to ambient air pollution. Sex differences may also reflect physiological differences, e.g. oestrogens may protect against the development of gastric cancer⁽²⁾. Since all major known risk factors including smoking, occupational exposures and *H. pylori* infection are more prevalent in men, residual confounding may have contributed to differences in men and women.

Residual confounding by occupational exposures with higher risk for gastric cancer such as shipyard, glass industry, manufacture of asbestos or asbestos cement and asbestos insulation could play a role⁽⁵⁾. although the frequency of these occupations in most of our general population samples is likely low.

DCH the second largest cohort has detailed information on occupational exposures. However, adjustment for this exposure (adding it to model1) did not change the effect estimate notably (only from 2.8 to 2.77) and it seems therefore unlikely that occupational exposure could cause the observed differences between men and women We furthermore did not find any consistent differences in HRs

related to smoking status and individual level SES, suggesting that these factors unlikely were responsible for the observed difference between men and women.

Among the strengths of our study is that we analyzed data of over 300 000 subjects from large European cohorts with information about potential confounders. The participants were recruited from the general populations from around Europe with large variation in the air pollution levels. In addition, information on different anatomic location and histologic types was available which is relevant since the aetiology could differ in subtypes. However, in several cohorts the case numbers of these subtypes were too small for separate analyses. Data concerning cancer outcomes based on national and regional cancer registries were virtually complete. However, missing values for subtype classification may have distorted to some extent the distribution of the histological subgroups. Only the outcome data from Rome was not based on cancer registries. However, a sensitivity analysis excluding the SIDRIA Rome cohort did not result in any notable change in the effect estimate for the overall study (results not shown). Our analyses were adjusted for the most important potential risk factors (e.g. age, smoking, individual and area-level SES). Additional sensitivity analyses including alcohol consumption, ETS, intake of fruit, intake of meat and marital status revealed robustness of the association between PM_{2.5} and gastric cancer risk. *H. pylori* could be considered as potential confounder for gastric cancer. Unfortunately, we lacked information on *H. pylori* infection status. However, we think that strong confounding is unlikely because 1) there is evidence that *H. pylori* is only a determinant in non-cardia but not in cardia gastric cancer ⁽²⁸⁾ and 2) a correlation between air pollution and *H. pylori* infection is unlikely particularly as our study included a large number of cohorts in different study area settings. The limited impact of adjustment for available confounders, including smoking and individual level SES on the PM_{2.5} HRs further argues against major residual confounding. We were able to control for the major risk factors of gastric cancer such as smoking, diet and occupational exposure. It can be speculated whether residual confounding or biological differences may have contributed to differences in men and women.

As we performed multiple comparisons a chance result for one of the pollutants cannot be excluded. However, our results for PM_{2.5} were remarkably consistent. Only one of the cohort effect estimates did not reflect a positive association.

Major strengths of our study are the standardized exposure assessment and a common standardized statistical protocol for all cohorts. Data on air pollution for 2008-2011 was used developing LUR models, but applied to baseline addresses mainly 10-15 years earlier depending on the cohort. There is recent evidence that the spatial distribution of air pollution with NO₂ is relatively stable over 10-year periods⁽²⁹⁻³¹⁾ and spatial models for black smoke performed well even for extrapolating back to the 1960s⁽³²⁾. The LUR models were validated and previously linked to lung cancer and other cancer sites (Raaschou-Nielsen O 2013, Pedersen 2017, Andersen et al. 2017, Andersen et al. 2017). Most former studies were limited by either proxy variable for air pollution or cancer mortality as end-point.

In conclusion, this study using the largest study population to date suggests that ambient air pollution with PM_{2.5} contributes to increased risk of gastric cancer. For UADT cancer no increased risk was found.

This work was supported by: the German Cancer Aid [111010] to GW and GN; the European Community's Seventh Framework Program (FP7/2007-2011) projects ESCAPE [211250] and TRANSPHORM [243406]; the Danish Council for Independent Research [DFF-4004-00179] to MPedersen; Marie Curie Intra European Fellowship within the 7th European Community Framework Programme to MPlusquin; the Dutch Ministry of Public Health, Welfare and Sports (V.W.S.); Netherlands Cancer Registry (N.K.R.); LK Research Funds; Dutch Prevention Funds; Dutch ZON (Zorg Onderzoek Nederland); World Cancer Research Fund (WCRF); and Statistics Netherlands (The Netherlands); the Danish Cancer Society.

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