SOCIOECONOMIC POSITION AND GASTRIC CANCER RISK IN THE STOMACH CANCER POOLING (STOP) PROJECT

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Introduction

Low socioeconomic position (SEP) has been linked to noncommunicable diseases, including several cancers. SEP reflects the availability of cultural, material and social resources that translate into advantages in terms of decision making, social network, lifestyle habits and also access to health services. SEP can be measured by a series of indicators, including education, occupation and income. These indicators are correlated but each of them measures different aspects of the socioeconomic stratification [1]. Education captures the intellectual assets of individuals besides the socioeconomic conditions in childhood and adolescence and also represents the opportunity to access to higher level jobs. Occupation reflects the privileges related to social standing, material resources and job-related risk factors; income is related to material resources, better living conditions and healthy environment.

The Stomach Cancer Pooling (StoP) Project is an international consortium of case-control (CC), including nested CC, studies on gastric cancer (GC) started in 2012 [2]. This consortium joins together scientists from several areas of the world aimed to study the role of lifestyle, dietary habits and genetic determinants in GC aetiology, through an individual participant data meta-analysis (IPD-MA). The latest StoP dataset release (version 3) includes 33 studies for a total of 12,753 stomach cancer cases and 30,682 controls. Its uniquely large sample size and access to raw patient-level data allowing centralized data harmonization are among the major strengths of the StoP Project [2].

In 2017, the center of Milan proposed to the Scientific Committee of the Stop Project a study on SEP and GC risk.

Aims

The first phase of the study aimed at i) quantifying the association between low SEP, as measured by education and income, and GC risk in the StoP Project, ii) studying the relation according to cancer subsite, histological subtype and in strata of geographic area or macroeconomic measure of income inequality of the country where the study was conducted. In a second phase, we will evaluate the mediation effect of some risk factors for GC that are more frequent in people with low SEP (i.e. *Helicobacter pylori* infection, tobacco smoking, heavy alcohol drinking, obesity and diet rich in salt and processed meat).

Methods

A two-stage approach was adopted. We firstly estimated study-specific odds ratios (ORs) and the corresponding 95% confidence intervals (CIs) using multivariable unconditional logistic regression models. Polytomous unconditional logistic regression models were fitted when analyzing the association by cancer subsite and histological type. We applied multiple imputations using full chained equations to avoid data loss due to sporadically missing values in study-specific covariates. Under the missing at random assumption, five imputed datasets were generated for each study, with missing values filled in with a set of plausible values drawn from the posterior predictive distribution of the missing data, conditional on the observed data. The imputation models were congenial with the analysis models and included the same set of covariates plus the case–control status. Study-specific regression coefficients and their standard errors were obtained through the Rubin's rule. In the second stage, summary (pooled) effect estimates were computed using a random-effect model.

Education was standardized across studies using the International Standard Classification of Education (ISCED 2011) of the UNESCO, an international reference classification that facilitates comparisons of education systems across countries. We defined three categories: (i) *low education level*, including early childhood and primary education (ISCED 0–1); (ii) *intermediate education level*, including secondary education (lower and upper) and postsecondary non-tertiary education (ISCED 2–4); (iii) *high education level*, including tertiary vocational education, often designed to provide participants with professional knowledge, skills and competencies and education leading to a university degree (ISCED 5–6).

Household income was harmonized starting from study questionnaires by grouping comparable levels into 4 categories, i.e. low, lower middle, upper middle and high.

To facilitate comparison with results from different studies, we estimated the relative index of inequality (RII) for both education and household income. The RII is a unique regression-based summary measure of social inequality that allows comparisons across countries with different distributions of the socioeconomic variables. It considers the size of the population in each socioeconomic level and their relative position in the socioeconomic scale. It represents the GC risk of subjects at the highest level of the socioeconomic hierarchy as compared to those in the lowest one.

The RII was defined as follows:

1. Within each study, for each of the k ordered levels (i = 1, …, k) of the SEP variable (i.e., education or household income), let c_i be the proportion of study subjects in class i or lower.
2. Then, for each class i = 1, …, k, let define $x_i = \frac{c_i + c_{i-1}}{2}$ as the mean rank, that is, the midpoint between the proportion of study subjects in class i (c_i) and those in the previous one (c_{i-1}).
3. The RII was then estimated by including the mean rank x_i as explanatory variable in the models used to derive the ORs instead of the original SEP variable.

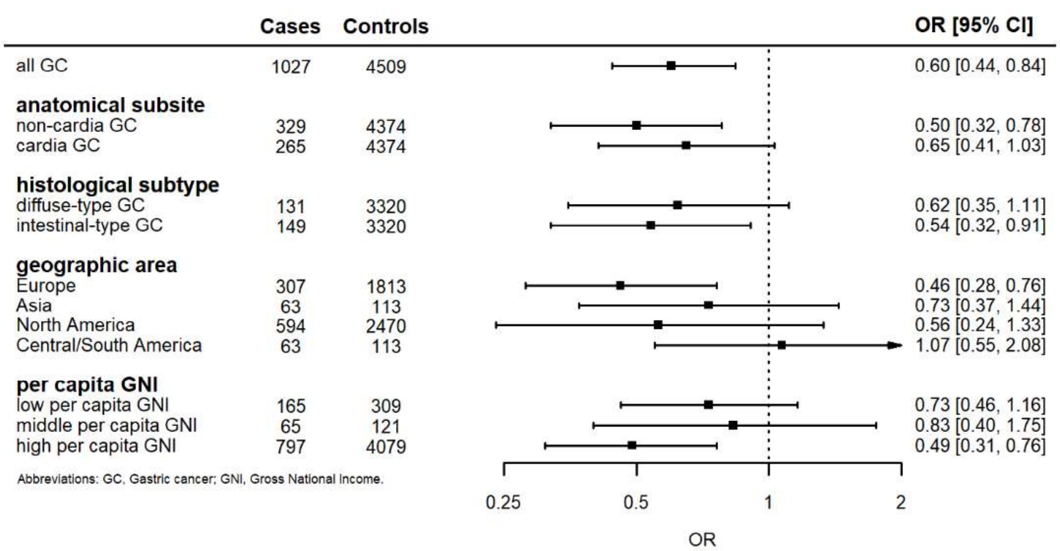
Models included terms for age, sex, alcohol drinking (never, ≤1 drink per day, >1 to ≤4 drinks/day and >4 drinks/day), tobacco smoking (never, former, current ≤10 cigarettes/day, >10 to ≤20 cigarettes/day, and >20 cigarettes/day), race/ethnicity (White, Hispanic/Latino, Black/African American, other), fruit and vegetable consumption (study-specific tertiles) and study centre (for multicentric studies).

Results

We used data from the second release of the StoP project dataset. A total of 25 case-control studies with available data for education or income (11 from European countries, 6 from Asian countries, 3 from North and 5 from Central/South American countries) for a total of 10,290 GC cases and 26,153 controls were considered [3]. Compared to low educational level (ISCED 0–1), both intermediate (ISCED 2–4) and high

(ISCED 5–6) educational levels were significantly associated with reduced GC risk, being the ORs from the fully adjusted models 0.68 (95% CI, 0.55–0.84) and 0.60 (95% CI, 0.44–0.84), respectively. The corresponding pooled RII was equal to 0.45 (95% CI, 0.29–0.69). Similar results emerged when using household income as a proxy for the SEP, with a significantly reduced GC risk in the highest as compared to the lowest household income category (OR 0.65, 95% CI, 0.48–0.89). The corresponding RII was 0.40 (95% CI, 0.22–0.72).
Results according to anatomical subsite, histological subtype, geographic area and study per capita GNI for highly (ISCED 5-6) as compared to less educated subjects (ISCED 0-1) are presented in Figure 1. In the analysis by cancer subsite, a strong inverse association was observed both for noncardia (highest vs. lowest level education: OR 0.50, 95% CI, 0.32–0.78) and cardia GC (OR 0.65, 95% CI, 0.41–1.03). Higher level of education was inversely associated with both diffuse (OR 0.62, 95% CI, 0.35–1.11) and intestinal-type (OR 0.54, 95% CI, 0.32–0.91) GC risk. The association was null when considering the studies from Central/South America (highest vs. lowest level education: OR 1.07, 95% CI, 0.55–2.08). There was a stronger significant inverse relationship between educational attainment and GC risk in studies from countries with high per capita GNI (OR 0.49, 95% CI, 0.31–0.76) as compared to those with middle (OR 0.83, 95% CI, 0.40–1.75) and low (OR 0.73, 95% CI, 0.46-1.16) per capita GNI.

Figure 1. *Selected results from stratified analyses for highly (ISCED 5-6) as compared to less educated subjects (ISCED 0-1).*



Conclusions

This uniquely large individual participant data meta-analysis provides a precise estimate of the strong inverse relationship between SEP and GC risk. We found a decreased GC risk among individuals with intermediate and high education levels as compared to those in the lowest level. Similar results emerged when we used household income as a proxy for the SEP. Our data call for public health interventions to reduce GC risk among the more vulnerable groups of the population. From the medical statistician perspective, the StoP project offers several opportunities of research related to methodological needs, including the management of systematically missing confounding factors, i.e. variables not collected in one or more studies. In the next phase of the study we will estimate the direct and indirect effects of SEP on GC risk via other GC risk factors through causal mediation analysis. This will give further insights into the mechanisms underlying the socioeconomic disparities in GC risk.

References

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