

Socioeconomic effect of education on pancreatic cancer risk in Western Europe: an update on the EPIC cohort Study

Social effect on pancreatic cancer risk updated in Europe

Abstract 249 words

Aim: To analyze the potential effect of social inequality on pancreatic cancer (PC) risk in Western Europe, by re-assessing the association within the European Prospective Investigation into Cancer and Nutrition (EPIC) study, including a larger number of cases and an extended follow-up.

Methods: Data on highest education attained was gathered for 459,170 participants (70% women) from ten European countries. A relative index of inequality (RII) based on adult education was calculated for comparability across countries and generations. Cox regression models were applied to estimate relative inequality in PC risk, stratifying by age, gender, and center, and adjusting for known PC risk factors.

Results: A total of 1,223 incident PC cases were included after a mean follow-up of 13.9 (\pm 4.0) years. An inverse social trend was found in models adjusted for age, sex, and center for both sexes combined (HR = 1.27, 95% confidence interval (CI): 1.02 to 1.59), which was also significant among women (1.42, 1.05 to 1.92) but not among men. However, further adjusting the models by smoking intensity, alcohol consumption, body mass index, prevalent diabetes, and physical activity, led to an attenuation of the RII risk and loss of statistical significance.

Conclusion: The present re-analysis does not support the existence of an independent social inequality influence on pancreatic cancer risk in Western European women and men, using an index based on adult education, the most relevant social indicator linked to individual lifestyles, in a context of very low PC survival from (quasi) universal public health systems.

11Keywords: Pancreatic Cancer; Cohort Studies; Smoking; Alcohol; Diet; Physical Activity; Socioeconomic Status; Education; Europe; EPIC

Introduction

The incidence and mortality of pancreatic cancer (PC) have undergone a parallel rise in Europe and North America in the last decades [1]. Meanwhile, PC survival is among the lowest in cancer (5-15%), and treatment advances have been minimal, despite the high quality and near universal coverage of health systems in Western Europe.

It is established that most PC are non-inherited, although family history also conveys a higher disease risk [2]. Nevertheless, little is known on the etiopathogenesis of PC, and effective screening tests are lacking.

Previous literature suggests a causal role for body fatness and, probably, adult height, where an evidence for alcohol, red or processed meat, and other dietary factors is limited or inconclusive [2]. The established PC risk factors are tobacco smoking, diabetes, and chronic pancreatitis [3].

Social determinants are linked to lifestyle cancer risk factors. However, a previous study on the association of PC with socioeconomic status within the European Prospective Investigation into Cancer and Nutrition (EPIC) was inconclusive [4]. This is the reason why we re-analyze this association including a larger number of cases and a longer follow-up using updated end-point data from the EPIC cohort.

Methods

Details on study methods and sample characteristics can be found elsewhere [4][5]. EPIC recruited volunteers from 10 European countries between 1992 and 2000, who were 35 to 70 years old at baseline. A relative index of inequality (RII) was estimated based on an educational ranking of individuals within each sex, age groups and center [4]. Of the 491,992 participants without prevalent cancer, those without baseline lifestyle or dietary information (n=6,259), extreme energy reporters (n=9,573), and individuals with missing data on education (n=16,931, including 19 PC cases) were excluded. Furthermore, participants who developed a different primary cancer prior to a pancreatic and neuroendocrine cancer (n=54) or non-malignant tumors (n=5) were censored at the date

of the event, leaving a final sample of 457,947 non-cases and 1,223 PC cases, with a mean follow-up of 13.9 (\pm 4.0) years (6,401,413 person-years) (Supplemental Table 1).

The RII was estimated through Cox regression with age as the time variable. Effect modification was evaluated by sex, age, BMI, smoking, alcohol, diabetes, and European region. Interactions were assessed using likelihood ratio tests. Sensitivity analyses were conducted to test the robustness of results against potential biases due to reverse causation or residual confounding.

Analyses were conducted using R version 3.3.2, and 2-sided p -values < 0.05 were considered statistically significant.

Results

Table 1 shows baseline participants' characteristics by educational rank. An inverse and statistically significant social trend was found in models adjusted for age, sex, and center for both sexes combined (RII = 1.27, 95% confidence interval (CI): 1.02 -1.59), which was stronger among women (HR = 1.42, 95% CI, 1.05-1.92) (Table 2). Multivariate adjustment attenuated RII estimates causing the loss of statistical significance. Results were similar when considering education as the exposure.

There was no effect modification in stratified analysis (Supplemental table 2). Sensitivity analyses adding new variables or excluding participants caused minor attenuations, which remained not significant (Supplemental table 2). Country-wise exclusion of participants resulted in a significant RII when excluding The Netherlands (RII=1.29, 95% CI 1.02-1.63) (Supplemental table 3).

Discussion

Education is the most common individual measure of social position since it allows classifying all individuals from young adulthood. Our results do not endorse a social stratification of PC risk in Europe, after accounting for major potential confounders.

We cannot discard plausible generation effects and misclassification due to the differences across educational systems. Furthermore, the assumption that all educational categories are hierarchically ordered is not always straightforward, as for vocational and secondary education. However, the alternative use of education as the exposure, and the sensitivity analyses conducted exhibited similar associations, supporting the robustness of results. Grouping secondary and vocational education did not result in higher PC risk (Table 2), and the comparison of extreme levels (university versus primary or lower) was not significant either.

Our results are in agreement with an earlier study evaluating the occupational status of UK's government employees, which did not obtain a significant risk of PC among the least affluent [6]. On the contrary, a cohort study performed in Norway found higher risk of PC in farmers versus low occupational groups, which did not change after lifestyle adjustments [7].

Among the limitations, we had no data on developmental factors affecting linear growth [2]. Nevertheless, a previous case-control study evaluating serum IGF-I and IGFBP-3 concentrations was unable to support a role for the IGF signaling axis on PC risk [8]. Finally, we did not have information on family history (PC is more frequent among family members). However, it is established that over 90% of incident PC are sporadic (mainly attributable to genetic mutations or epigenetic dysregulation), and not inherited.

Conclusions

These results do not support an association between education and risk of pancreatic cancer.

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Conflict of interest statement

None declared.

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