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Socioeconomic Effect of Education on Pancreatic Cancer Risk in Western Europe: An Update on the EPIC Cohorts Study

Lluís Cirera[1,2,3], José María Huerta[1,2], María Dolores Chirlaque[1,2,3], Kim Overvad[4], Martin Lindström[5], Sara Regnér[5], Anne Tjønneland[6,7], Marie-Christine Boutron-Ruault[8,9], Vinciane Rebours[10,11], Guy Fagherazzi[8,9], Verena A. Katzke[12], Heiner Boeing[13], Eleni Peppa[14], Antonia Trichopoulou[14], Elissavet Valanou[14], Domenico Palli[15], Sara Grioni[16], Salvatore Panico[17], Rosario Tumino[18], Fulvio Ricceri[19,20], Carla van Gils[21], Roel C.H. Vermeulen[21,22], Guri Skeie[23], Tonje Braaten[23], Elisabete Weiderpass[23–26], Susana Merino[27], María José Sánchez[28], Nerea Larrañaga[2,29], Eva Ardanaz[2,30,31], Malin Sund[32], Kay-Tee Khaw[33], Timothy J. Key[34], Mazda Jenab[35], Sabine Naudin[35], Neil Murphy[35], Dagfinn Aune[36], Heather Ward[36], Elio Riboli[36], Bas Bueno-de-Mesquita[37–40], Carmen Navarro[3], and Eric J. Duell[41]

Abstract

Background: To analyze the potential effect of social inequality on pancreatic cancer risk in Western Europe, by reassessing 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 were gathered for 459,170 participants (70% women) from 10 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 pancreatic cancer risk, stratifying by age, gender, and center, and adjusting for known pancreatic cancer risk factors.

Results: A total of 1,223 incident pancreatic cancer cases were included after a mean follow-up of 13.9 (±4.0) years. An inverse social trend was found in models adjusted for age, sex, and center for both sexes [HR of RII, 1.27; 95% confidence interval (CI), 1.02–1.59], which was also significant among women (HR, 1.42; 95% CI, 1.05–1.92). Further adjusting 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.

Conclusions: The present reanalysis does not sustain 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 pancreatic cancer survival from (quasi) universal public health systems.

Impact: The results do not support an association between education and risk of pancreatic cancer.

[1]Department of Epidemiology, Murcia Regional Health Council, IMIB-Arrixaca, Murcia, Spain. [2]CIBER de Epidemiología y Salud Pública (CIBERESP), Madrid, Spain. [3]Department of Health and Social Sciences, University of Murcia, Murcia, Spain. [4]Department of Public Health, Aarhus University, Aarhus, Denmark. [5]Department of Clinical Sciences, Social Medicine and Health Policy, Lund University, Malmö, Sweden. [6]Diet, Genes and Environment, Danish Cancer Society Research Center, Copenhagen, Denmark. [7]Department of Public Health, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark. [8]CESP, Faculté de Médecine - Université Paris-Sud, Faculté de Médecine - UVSQ, INSERM, Université Paris-Saclay, Villejuif, France. [9]Gustave Roussy Institute, Villejuif, France. [10]Pancreatology Unit, Beaujon Hospital, Clichy, France. [11]INSERM - UMR 1149, University Paris 7, France. [12]German Cancer Research Center (DKFZ), Heidelberg, Germany. [13]Department of Epidemiology German Institute of Human Nutrition (DIfE), Potsdam-Rehbrücke, Germany. [14]Hellenic Health Foundation, Athens, Greece. [15]Cancer Risk Factors and Life-Style Epidemiology Unit, Institute for Cancer Research, Prevention and Clinical Network - ISPRO, Florence, Italy. [16]Epidemiology and Prevention Unit, Fondazione IRCCS Istituto Nazionale dei Tumori di Milano, Milano, Italy. [17]Dipartimento di Medicina Clinica e Chirurgia, Federico ii University, Naples, Italy. [18]Department of Cancer Registry and Histopathology, "Civic - M.P. Arezzo" Hospital, ASP Ragusa, Italy. [19]Department of Clinical and Biological Sciences, University of Turin, Italy. [20]Unit of Epidemiology, Regional Health Service ASL TO3, Grugliasco (TO), Italy. [21]Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, the Netherlands. [22]Environmental Epidemiology Division, Institute for Risk Assessment Sciences, Utrecht University, Utrecht, the Netherlands. [23]Department of Community Medicine, University of Tromsø, The Arctic University of Norway, Tromsø, Norway. [24]Department of Research, Cancer Registry of Norway, Institute of Population-Based Cancer Research, Oslo, Norway. [25]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden. [26]Genetic Epidemiology Group, Folkhälsan Research Center, and Faculty of Medicine, Helsinki University, Helsinki, Finland. [27]Public Health Directorate, Regional Government of Asturias, Oviedo, Spain. [28]Escuela Andaluza de Salud Pública, Instituto de Investigación Biosanitaria ibs.GRANADA, Hospitales Universitarios de Granada/Universidad de Granada, Granada, Spain. [29]Public Health Division of Gipuzkoa, Regional Government of the Basque Country, Donostia, Spain. [30]Navarra Public Health Institute, Pamplona, Spain. [31]IdiSNA, Navarra Institute for Health Research, Pamplona, Spain. [32]Department of Public Health, Aarhus University, Aarhus, Denmark. [33]University of Cambridge,

Introduction

The incidence and mortality of pancreatic cancer have undergone a parallel rise in Europe and North America in the last decades (1). Meanwhile, pancreatic cancer 5-year survival is among the lowest of the common cancers (7%), 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 pancreatic cancer are noninherited, although family history also conveys a higher disease risk (2). Nevertheless, little is known on the etiopathogenesis of pancreatic cancer, 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 pancreatic cancer risk factors are tobacco smoking, body mass index (BMI), diabetes, and chronic pancreatitis (3).

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

Materials and 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 on the basis of 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 pancreatic cancer cases) were excluded. Furthermore, participants who developed a different primary cancer prior to a pancreatic and neuroendocrine cancer ($n = 54$) or nonmalignant tumors ($n = 5$) were censored at the date of the event, leaving a final sample of 457,947 noncases and 1,223 pancreatic cancer cases, with a mean follow-up of 13.9 ($\pm$ 4.0) years and 6,401,413 person-years (Supplementary Table S1).

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 two-sided P values <0.05 were considered statistically significant.

Results

Table 1 shows baseline participants' characteristics by the educational ranks of RII. An inverse and statistically significant social trend was found in models adjusted for age, sex, and center for both sexes combined [HR of 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 (Supplementary table S2). Sensitivity analyses adding new variables or excluding participants caused minor attenuations, which remained not significant (Supplementary table S2). Country-wise exclusion of participants resulted in a significant RII when excluding the Netherlands (RII, 1.29; 95% CI, 1.02–1.63; Supplementary table S3).

Discussion

Education is the most common individual measure of social position because it allows classifying all individuals from young adulthood. Our results do not endorse a social stratification of pancreatic cancer risk in Western 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 pancreatic cancer 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 United Kingdom's government employees, which did not obtain a significant risk of pancreatic cancer among

School of Clinical Medicine Addenbrooke's Hospital, Cambridge, United Kingdom. [34]Nuffield Department of Population Health, Cancer Epidemiology Unit, University of Oxford, Oxford, United Kingdom. [35]Section of Nutrition and Metabolism, International Agency for Research on Cancer, World Health Organization, Lyon, France. [36]Department of Epidemiology and Biostatistics, Faculty of Medicine, School of Public Health, Imperial College London, United Kingdom. [37]Department for Determinants of Chronic Diseases (DCD), National Institute for Public Health and the Environment (RIVM), Bilthoven, the Netherlands. [38]Department of Gastroenterology and Hepatology, University Medical Centre, Utrecht, the Netherlands. [39]Department of Epidemiology and Biostatistics, Faculty of Medicine, School of Public Health, Imperial College London, United Kingdom. [40]Department of Social and Preventive Medicine, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia. [41]Unit of Nutrition and Cancer, Cancer Epidemiology Research Program, Catalan Institute of Oncology (ICO-IDIBELL), L'Hospitalet de Llobregat, Spain.

Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

Corresponding Author: Lluís Cirera, Regional Health Council of Murcia, Ronda Levante 11, Murcia, E30008, Spain. Phone: 34-968-365747; Fax: 34-968-366656; E-mail: luis.cirera@carm.es

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Table 1. Baseline participants' characteristics in the EPIC Study by the RII

	RII[a]			
	(0–0.25)	**(0.25–0.50)**	**(0.50–0.75)**	**(0.75–1.00)**
N	112,542	99,384	149,168	98,135
Person-years/cases	1,544,380/270	1,447,272/260	2,031,255/337	1,378,506/356
Women	79,201 (70.4)	66,520 (66.9)	110,843 (74.3)	64,274 (65.5)
Age (years)	51.2 (8.5)	48.7 (11.1)	51.6 (9.7)	52.5 (9.5)
BMI (kg/m^2)	24.6 (3.8)	24.9 (4.0)	26.0 (4.6)	26.1 (4.3)
Normal weight	67,718 (60.2)	56,077 (56.4)	69,011 (46.3)	43,954 (44.8)
Overweight	35,450 (31.5)	33,326 (33.5)	53,340 (35.8)	38,389 (39.1)
Obese	9,374 (8.3)	9,981 (10.0)	26,817 (18.0)	15,792 (16.1)
Smoking				
Never	54,101 (48.1)	47,451 (47.7)	80,811 (54.2)	42,639 (43.4)
Former	33,065 (29.4)	27,929 (28.1)	33,824 (22.7)	26,885 (27.4)
Current	22,858 (20.3)	23,105 (23.2)	31,396 (21.0)	27,215 (27.7)
Physically inactive	19,420 (17.3)	16,633 (16.7)	38,757 (26.0)	19,998 (20.4)
Diabetes	2,145 (2.0)	1,645 (1.8)	5,492 (3.9)	2,842 (3.1)
Energy intake (kcal/day)	2,109 (596)	2,054 (606)	2,075 (629)	2,070 (649)
Fruit and vegetable intake (g/day)	455.1 (274.6)	409.5 (251.7)	484.6 (278.9)	390.6 (254.3)
Red and processed meat intake (g/day)	75.8 (48.2)	68.5 (49.7)	76.6 (50.9)	80.3 (54.5)
Alcohol consumers	101,183 (89.9)	91,415 (92.0)	118,897 (79.7)	85,003 (86.6)
Alcohol consumption (g/day)[b]	14.98542 (17.548)	12.80948 (15.672)	13.88367 (18.631)	12.46815 (17.928)

NOTE: Values are mean and SD or numbers and percentages.
[a]Educational rank from most educated (0) to least educated (1), corresponding to the mean proportion of the population with a higher education within the corresponding group of sex, age category, and center.
[b]Mean intake estimated among alcohol consumers only.

the least affluent (6). On the contrary, a cohort study performed in Norway found higher risk of pancreatic cancer 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 insulin-like growth factor I (IGF-I) and IGFBP-3 concentrations was unable to support a role for the IGF signaling axis on pancreatic cancer risk (8). Finally, we did not have information on family history (pancreatic cancer is more frequent among family members). However, it is established that over 90% of incident pancreatic cancers 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.

Table 2. Association between education and the RII with pancreatic cancer in the EPIC Cohorts Study

		Person-years	**Cases**	**Model 1 HR (95% CI)**	**Model 2 HR (95% CI)**
All	University	1,570,473	233	1 (ref.)	1 (ref.)
	Secondary or vocational	2,842,462	479	1.08 (0.92–1.28)	1.05 (0.89–1.23)
	Primary or less	1,988,478	511	1.20 (1.01–1.42)	1.12 (0.94–1.33)
	$P_{\text{linear trend}}$			0.036	0.201
	RII	6,401,413	1,223	1.27 (1.02–1.59)	1.17 (0.93–1.46)
	$P_{\text{linear trend}}$			0.030	0.173
	$P_{\text{nonlinear trend}}$			0.113	0.464
Women	University	1,050,615	104	1 (ref.)	1 (ref.)
	Secondary or vocational	2,091,455	291	1.06 (0.84–1.35)	1.05 (0.83–1.34)
	Primary or less	1,332,521	290	1.27 (0.98–1.64)	1.18 (0.91–1.54)
	$P_{\text{linear trend}}$			0.046	0.164
	RII	4,474,592	685	1.42 (1.05–1.92)	1.29 (0.95–1.75)
	$P_{\text{linear trend}}$			0.022	0.103
	$P_{\text{nonlinear trend}}$			0.113	0.331
Men	University	519,858	129	1 (ref.)	1 (ref.)
	Secondary or vocational	751,007	188	1.12 (0.89–1.41)	1.04 (0.83–1.31)
	Primary or less	655,957	221	1.13 (0.89–1.44)	1.03 (0.81–1.31)
	$P_{\text{linear trend}}$			0.330	0.735
	RII	1,926,821	538	1.12 (0.81–1.54)	1.00 (0.72–1.38)
	$P_{\text{linear trend}}$			0.488	0.981
	$P_{\text{nonlinear trend}}$			0.729	0.923
	$P_{\text{sex interaction}}$			0.310	0.249

NOTE: Model 1, adjusted by sex and stratified by center and baseline age categories; model 2, as model 1, plus further adjustment by smoking intensity, alcohol consumption, BMI, prevalent diabetes, and physical activity. The RII expresses the ratio of the expected pancreatic cancer risk between the most educated (reference) and the least educated participants in the cohorts.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: L. Cirera, J.M. Huerta, M.-D. Chirlaque, K. Overvad, A. Tjonneland, M.-C. Boutron-Ruault, H. Boeing, R. Tumino, E. Weiderpass, N. Larrañaga, K.-T. Khaw, M. Jenab, B. Bueno-de-Mesquita

Development of methodology: L. Cirera, J.M. Huerta, M.-D. Chirlaque, E. Weiderpass, N. Larrañaga, M. Jenab, B. Bueno-de-Mesquita

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): M.-D. Chirlaque, K. Overvad, M. Lindstrom, S. Regner, A. Tjonneland, M.-C. Boutron-Ruault, V. Rebours, G. Fagherazzi, H. Boeing, A. Trichopoulou, D. Palli, S. Panico, R. Tumino, F. Ricceri, R. Vermeulen, G. Skeie, E. Weiderpass, S. Merino, M.J. Sánchez, N. Larrañaga, M. Sund, K.-T. Khaw, T.J. Key, B. Bueno-de-Mesquita, C. Navarro

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): L. Cirera, J.M. Huerta, M.-D. Chirlaque, E. Weiderpass, N. Larrañaga, B. Bueno-de-Mesquita

Writing, review, and/or revision of the manuscript: L. Cirera, J.M. Huerta, M.-D. Chirlaque, K. Overvad, M. Lindstrom, S. Regner, A. Tjonneland, M.-C. Boutron-Ruault, G. Fagherazzi, V.A. Katzke, H. Boeing, E. Peppa, A. Trichopoulou, D. Palli, S. Grioni, S. Panico, R. Tumino, F. Ricceri, C. van Gils, R. Vermeulen, G. Skeie, T. Braaten, E. Weiderpass, M.J. Sánchez, N. Larrañaga, M. Sund, K.-T. Khaw, T.J. Key, M. Jenab, S. Naudin, N. Murphy, D. Aune, H.A. Ward, E. Riboli, B. Bueno-de-Mesquita, C. Navarro, E.J. Duell

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): S. Regner, H. Boeing, R. Tumino, E. Weiderpass, N. Larrañaga, K.-T. Khaw

Study supervision: L. Cirera, M.-D. Chirlaque, R. Tumino, E. Weiderpass, N. Larrañaga, B. Bueno-de-Mesquita, C. Navarro

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